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VOLUME 83 NUMBER 3

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

September, 1948

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PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

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BULLETIN
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This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

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THE JOHNS HOPKINS PRESS
BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Postoffice. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.

DIFFERENTIAL DIAGNOSIS OF TUMORS AT THE CEREBELLOPONTILE RECESS

ANTONIO GONZALEZ REVILLA*

From the Department of Surgery, Division of Neurosurgery, The Johns Hopkins Hospital

Received for Publication July 28, 1947

The diagnosis of a lesion occupying the cerebellopontile recess is relatively easy. The clinical differentiation of these lesions represents, however, a difficult problem which frequently is not solved until a microscopic examination of the pathological specimen is undertaken. We have confronted this diagnostic dilemma during our previous study on the neurinomas (8) and decided, therefore, to analyze the different tumors occurring in this location and to point out, whenever possible, their main differential diagnostic features.

As seen in the accompanying table a total of two hundred and five tumors of the cerebellopontile recess were verified at operation at the Johns Hopkins Hospital from 1926 to 1945. Most of these operations were performed by Dr. Walter E. Dandy. The most common type was the neurinoma which comprised 78 per cent of the series. The remaining 22 per cent of neoplasms will be discussed in detail in this presentation as we have analyzed the neurinoma group elsewhere (8). Abscesses have been included in the series because clinically they may behave like any other tumor at the angle. Aneurysms and other vascular abnormalities purposely have not been considered as we wish to limit ourselves at this time to lesions which may be attacked surgically with certain degrees of success. There are many other lesions at the recess not included in this paper, such as the infectious granulomas, the osteomas, and the so-called chronic cisternal arachnoiditis. None of these were found in the hospital records during the period under consideration. The classification of Evans and Courville (6) on the subject is quite complete and the reader is therefore referred to their paper.

* At present at the Department of Neurosurgery, Hospital Santo Tomas, Panama, R. of P.

NEURINOMAS

Only the outstanding characteristics of the neurinomas shall be discussed because, as we stated before, they have been analyzed in detail in a previous communication (8).

a. Unilateral acoustic neurinomas without peripheral neurofibromatosis: one hundred and forty five such tumors were found in this

TABLE 1

Cerebellopontile tumors. The Johns Hopkins Hospital 1926–1945

TYPE OF TUMOR	NO. CASES	%
Neurinomas	160	78.0
a. Unilateral acoustic	145	
b. Bilateral acoustic	6	
c. Unilateral acoustic with peripheral neurofibromatosis	3	
d. Neurinomas Vth N	3	
e. Neurinomas Xth N	2	
f. Neurinomas XIth N	1	
Cholesteatomas	13	6.3
Meningiomas	13	6.3
Gliomas:	12	5.9
a. Astrocytoma	5	
b. Astroblastoma	1	
c. Medulloblastoma	3	
d. Ependymoma	2	
e. Glioblastoma multiforme	1	
Abscesses	4	1.9
Miscellaneous tumors	3	1.6
a. Sarcoma of meninges	1	
b. Carotid body tumor	1	
c. Malignant melanoma	1	
Total	205	100.0

series, 62.8 per cent of which occurred in females and 37.2 per cent in males. The average age at the onset of symptoms was 39.6 years, the youngest 12 and the oldest 69. The average duration of symptoms was 4.5 years, the shortest 8 weeks, and the longest 20 years. The chronological order of symptoms postulated by Cushing (2) was present in only 31 per cent of the cases. In 30 per cent the Vth N. was affected shortly after the onset of auditory and labyrinthine disturbances. Incoordination and other manifestations of involvement

of the cerebellar pathways followed symptoms referable to the VIIIth N. in 20.7 per cent. Headaches, occipital pains or suboccipital discomforts preceded even the auditory manifestations in 12.4 per cent. In 6 per cent no definite pattern was followed.

In the greatest number of instances there was subjective and objective evidence of involvement of the VIIIth and Vth nerves as well as the cerebellar pathways. The VIIIth N. was involved in every case either by affection of both components or by solitary involvement of either the cochlear or vestibular branches. In certain instances only the VIIIth N. was affected, the patients presenting on admission Meniere's syndrome, which although uncommon with tumors at the angle does occur. Tic douloureux was the only complaint in many instances, but in this series was always accompanied by some loss of hearing, with the exception of one case. This hearing deficit may be easily overlooked because of the frequency of hearing loss at this age. Audiometer and vestibular tests are therefore in order in every patient with tic douloureux. X-ray evidence of destruction of the porus acusticus was present in 50 per cent of the cases and when absent was not therefore absolute proof against a positive diagnosis. Although papilledema has been mentioned by others (9) as a very common finding in acoustic tumors, it was found in only 66.5 per cent of this group.

b. Unilateral acoustic neurinomas and peripheral neurofibromatosis: these have been considered separately from the preceding group as they differ in some respects. Only three such cases were found. The average age at the onset of intracranial disturbances was far below the average age of patients with solitary neurinomas; e.g., 14.3 years, the youngest 9 and the oldest 20. The duration of symptoms was 10 years, twice as long as in the preceding group.

There was no specific chronological order of symptoms but the auditory, trigeminal and cerebellar manifestations were predominant. The first two were constantly present objectively. Only one patient showed involvement of the spinal cord.

c. Bilateral Acoustic Neurinomas: six such tumors were encountered. Males and females were equally affected. In two of these patients, both sisters, there was a history of bilateral acoustic neurinomas on the maternal side of the family in approximately thirty-

five members since the eighteenth century. Their relationship with peripheral von Recklinghausen's disease seems more obvious than in the unilateral neurinomas. Three cases showed evidence of peripheral involvement elsewhere in the body.

The average age at the onset of symptoms was 17.8 years, the youngest 9 and the oldest 29. These figures approach those found in unilateral acoustic tumors with evidence of peripheral neurofibromatosis. The duration of symptoms, however, was much shorter; e.g., 5 years, approaching the duration of symptoms in the unilateral neurinomas without von Recklinghausen's disease.

The symptomatology was typically characterized by bilateral diminution of hearing which was corroborated objectively in all. Bilateral involvement of one or more cranial nerves and cerebellar pathways was invariably present. X-ray of the skull showed unilateral or bilateral erosion of the porus acusticus.

d. Neurinomas of the Vth Nerve: three cases comprise this group. There was no evidence of peripheral neurofibromatosis. The age of onset was much later than in the solitary acoustic neurinomas; e. g. 47 years, and the average duration was exactly the same as in the acoustic neurinomas with evidence of peripheral neurofibromatosis.

Upon admission to the hospital these cases were clinically indistinguishable from the unilateral acoustic neurinomas. The only important differential diagnostic point was the fact that trigeminal symptoms preceded auditory and labyrinthine disturbances by an average of 4.5 years. In two of these patients the initial and predominant complaint was that of tic douloureux, and this again stresses (4, 5) the importance of the relationship of tumors at the cerebellopontile recess to trigeminal neuralgia.

e. Neurinomas of the Xth Nerve: two such cases were found in this series. The age at the onset of symptoms was 29 and 53 years respectively and the duration of symptoms 1 and 7 years. The predominant and initial symptom was that of hoarseness which in one case was the only finding. Paresis of one vocal cord was corroborated on admission. Evidence of involvement of other cranial nerves may or may not be present. If hoarseness is associated with unilateral paralysis of the vocal cords a tumor of the Xth N. is a likely possibility.

f. Neurinomas of the XIth Nerve: only one case was encountered in

this group. The age at the appearance of symptoms was 63.5 years with a duration of $4\frac{1}{2}$ years. There was evidence of peripheral neurofibromatosis about 5 years previous before the onset of intracranial involvement. The initial symptom was gradual stiffness and atrophy of the left arm and shoulder girdle, followed 3 years later by suboccipital discomfort, disphagia, hoarseness and incontinence. On admission the patient showed involvement of the IXth, Xth, XIth and XIIth cranial nerves and ipsilateral cerebellar signs. There was no impairment of hearing. The presence of a neurinoma originating from the XIth N. was disclosed at operation.

CHOLESTEATOMAS OR PEARLY BODY TUMORS

Thirteen such cases (6.3 per cent) were present in this series, exactly the same number as the meningiomas which will be discussed later. Females were affected more frequently than males in a ratio of 10:3. In one case the symptomatology started with trauma to the head on the affected side with loss of consciousness. A history of acute otitis media on the same side as the lesion was elicited in another. In the latter case there were no symptoms referable to the ear and no obvious abnormalities could be elicited upon examining the VIIIth N. The left side was affected almost invariably, only two cases occurring on the right.

The average age of the patients on admission was 40.6 years, the oldest 60 and the youngest 13. The actual age at the onset was 33.3 years, the oldest 41 and the youngest 11. The average duration of symptoms was 7.3 years, the longest 23 years and the shortest 6 weeks.

Symptomatology: In ten cases the only symptom on admission was that of tic douloureux, one more case having been added since our previous communication (7). The chief complaint in these cases was that of paroxysmal, lancinating, intermittent pain occurring in one side of the face only, affecting the distribution of the three branches of the Vth N. in seven, the second and third branches in two, and the first and second in one. The pain was more frequent and more severe than in the usual cases with "idiopathic" tic douloureux and less apt to remit. None of these ten cases presented complaints referable to the ear. The remaining cases had initial symptoms involving the VIIIth N. Two complained of tinnitus and gradual diminution of

hearing on the affected side, and one complained of hearing deficit unaccompanied by tinnitus. Two of these cases had severe rotary vertigo coming on in periodic attacks with nausea and vomiting. A diagnosis of Meniere's disease was made and the tumors were found incidentally upon sectioning the VIIIth N. through a unilateral cerebellar approach. Cerebellar manifestations were present in three cases. In two they followed the auditory disturbances, and in one the trigeminal complaints. Headaches were similarly quite rare and never represented an initial or predominant symptom. They were described as suboccipital in two and bifrontal in one. Subjective involvement of the VIIth N. was even less frequent and was elicited in two cases. In one there was just a peripheral type of facial weakness, and in the other clonic contractions of the facial muscles on the affected side. Dysphagia was present in one case, occurring rather late in the course of the illness, in addition to auditory disturbances.

Signs: The state of consciousness was good in every case. Vision was well preserved except in one case with predominant auditory disturbances in which the patient was completely blind on admission and showed on fundoscopic examination secondary optic atrophy. The fundi and peripheral fields were completely normal in the remaining cases. No abnormalities of the IIIrd, IVth and VIth cranial nerves could be elicited in this group. Objectively disturbances of the Vth N. were found in four cases. These were characterized by diminished or absent corneal reflexes, hypalgesia and hypaesthesia in one or all of the three branches. Two of these occurred in patients complaining of tic douloureux and the other two in patients who had predominant auditory disturbances. Facial paralysis was infrequent and could be corroborated in only two cases, one of which had only trigeminal symptoms and in the other the auditory manifestations were outstanding. Loss of taste in the anterior two-thirds of the tongue on the affected side was elicited in one patient complaining of tic douloureux with no evidence of facial paralysis. Hearing was intact in all the cases complaining of tic douloureux, and the caloric test was similarly normal in all except one. In three patients with subjective involvement of the VIIIth N. the audiogram showed complete deafness in two and partial in one, the hearing deficit being neurogenic. Vestibular tests on the other hand were performed in

only one patient who showed a normal response. The rest of the cranial nerves were intact with the exception of one case with a hearing deficit who showed, in addition, ipsilateral palatal paralysis. Unilateral ataxia and horizontal nystagmus were present in the three cases with predominant VIIIth N. disturbances. Horizontal nystagmus alone was found in only one case with tic douloureux. Bilateral pyramidal signs were extremely rare, appearing in one of the cases with auditory disturbances. There were no sensory changes.

X-rays: Two patients with tic douloureux were suspected of having a tumor and X-rays of the skull were taken accordingly. Both of these were reported normal. Base films were taken in all patients with auditory disturbances. In one there was definite evidence of erosion of the internal acoustic meatus while the others were entirely negative.

Comments: In this group, as in the acoustic neurinomas, females were vastly more affected than males. The left side was almost invariably involved. The duration of symptoms was more prolonged than in the unilateral neurinomas of the VIIIth N. without peripheral neurofibromatosis. The most common symptom was that of lancinating pain in one side of the face, intermittent and paroxysmal in character, usually involving the distribution of the three branches of the trigeminal nerve. This pain was less apt to remit spontaneously than in the so-called "idiopathic" tic douloureux, and the intensity and frequency of the attacks were quite severe. Involvement of other cranial nerves was infrequent in spite of the relatively large size of these tumors at the recess. Auditory and labyrinthine manifestations were rare and when present tended to take the form of Meniere's disease. Subjective involvement of other cranial nerves or of the cerebellar pathways was practically absent. Objectively one was surprised at the paucity of signs. Papilledema was extremely rare. Only four cases showed objective evidence of affection of the Vth N. Clonic contractions of one side of the face and unilateral facial weakness occurred in isolated cases. Diminution of hearing was also quite rare. Cerebellar signs were very uncommon and pyramidal signs were almost nil. In most of these patients the true nature of the condition was not suspected as the diagnosis of either tic douloureux or Meniere's disease was made from the history and physical findings These tumors apparently produced little or no erosion of the porus acusticus as evi-

denced either by x-ray or at operation. When auditory or labyrinthine disturbances were present as the initial symptoms it was somewhat difficult to differentiate them clinically from the acoustic neurinomas. The essential differential points are the younger age of onset, the longer duration of symptoms, the absence of headaches and negative x-ray findings. The diagnosis of these lesions is extremely important since they are benign and easily extirpated. Not a single mortality was recorded in this group.

MENINGIOMAS

Thirteen cases (6.3 per cent) comprise this group. As noted before, they occurred with the same frequency as the pearly body tumors. Likewise, females were affected more often than males in the proportion of 10:3. No history of infection was elicited, but there was history of trauma to the head with loss of consciousness in one case. In contradistinction to the cholesteatomas the right side was affected almost invariably, only three cases occurring on the left.

The average age of the patients on admission was 50.3 years, the youngest 21 and the oldest 71. The average age of the appearance of symptoms was 46.3 years, the oldest 69 and the youngest 19. The average duration of symptoms was four years.

Symptomatology: Auditory and labyrinthine disturbances were the initial symptoms in six. Diminution of hearing was the most predominant subjective manifestation of VIIIth N. involvement, being present in eight. Tinnitus was less common, occurring in three cases, in two of which it was simultaneous with the hearing loss while it followed vestibular disturbances in one. Dizziness could be elicited in two, in one of which it was associated with hearing loss and in the other represented the only acoustic symptom. Similarly, true rotary vertigo was present in two cases, in one of which there was tinnitus without hearing loss, and in the other both tinnitus and hearing loss. The preoperative diagnosis of Meniere's disease was made in these two cases.

Trigeminal symptoms occurred as frequently as the auditory manifestations and were present in ten cases, representing the initial symptoms in four. The most predominant complaint was that of paroxysms of pain, which was elicited in five. Subjective numbness

of the face was present in the remainder. It is interesting to note that numbness and pain were not present together. The pain was more apt to remit and less frequent than in the pearly body tumors. Tic represented the initial symptom in four cases while numbness followed auditory disturbances in five. In one instance tic douloureux appeared simultaneously with the auditory disturbances.

The next most frequent symptom was that of cerebellar origin. It was present in eight and represented the initial symptom in two. Clumsiness of one arm or unsteadiness in walking was the usual complaint. It occurred simultaneously with trigeminal symptoms in one and followed disturbances of the VIIIth N. in six.

In contradistinction to the pearly body tumors, headaches were a common feature in the meningiomas and occurred in eight cases. It was the initial symptom in one and occurred initially either with the cerebellar or auditory manifestations in three. It is interesting to note that all cases complaining of numbness of the face had headaches, whereas only one case with tic douloureux complained of this symptom. Headaches were mostly suboccipital but in one case they were both frontal and occipital. Two patients complained of pain behind the ear. In half of the cases headaches were increased by coughing, straining or change of position.

Diminution of vision was present in almost 50 per cent of the cases, and one patient was blind on admission. This symptom came as a late manifestation. Involvement of other cranial nerves was rare. Clonic twitchings of the face on the affected side was present in one case who had predominantly auditory disturbances. Dysphagia and dysarthria, although late manifestations, were more frequent and occurred in four cases. There was no subjective evidence of pyramidal tract or sensory manifestations in the body or extremities. Hypothalamic symptoms such as obesity, somnolence, amenorrhea, polydypsia and polyuria were present in one case in whom the diagnosis of pituitary adenoma was suspected, but obviously these were due to pressure from a dilated third ventricle.

Signs: Two patients were drowsy on admission. Diminution of vision was corroborated in five, and one patient was completely blind. Bilateral papilledema was present in four. Secondary optic atrophy and profuse retinal hemorrhages in two. There was no significant

variation in the visual fields, and there were no disturbances of the extra-ocular movements.

The Vth N. was found to be objectively affected in seven cases. Unilateral sensory changes in the face with diminished or absent corneal reflexes were elicited in six, while bilateral involvement was corroborated in one. In two of these cases there was also involvement of the muscles of mastication. Only one patient complaining of tic douloureux showed any sensory loss on the face.

Facial paralysis was more common than in any of the preceding groups and was present in seven cases, partial in five and complete in two. In only one could loss of taste on the anterior two-thirds of the tongue without evidence of facial weakness be corroborated.

In nine cases there was either marked diminution or absence of hearing on the affected side. The hearing loss was unilateral in all but in one who showed bilateral diminution of hearing. An absent vestibular response accompanied every case with hearing deficit. One case with normal hearing showed no response to caloric stimulation. Paralysis of the palate was elicited in one.

Objective cerebellar manifestations were present in seven cases, being unilateral in five and bilateral in two. Horizontal nystagmus was predominant in six, while coarse nystagmus was present in only one case. Pyramidal signs were infrequent, appearing in two cases, unilateral and bilateral respectively. Sensory changes were even more uncommon and were present in one on the same side as the lesion.

X-rays were taken in six of these patients and only one showed destruction of the petrous pyramid. In two there was marked enlargement of the sella turcica and the remainder were normal.

At operation all the tumors were totally removed except in two instances in which there was extension of the neoplastic process to the middle and anterior fossae. The operative mortality was quite high, five of them dying immediately after the operation. In fact, the mortality in this group is the highest of the series. This may be explained by the extreme hardness, vascularity and proximity to the transverse sinus of most of these tumors, which make their removal a most arduous and hazardous procedure. Cushing (2) however, considers them one of the most favorable ones at the recess.

Comments: In conclusion, we have that females were vastly more

often affected than males. The average age at the onset of symptoms was 46.3 years with a duration of 4 years. The age at the onset was therefore in an older group than in the preceding ones, while the duration of symptoms approached closely the duration in the solitary acoustic neurinomas. The right side was predominantly affected. Auditory and labyrinthine disturbances represented the most common initial manifestation, and at times they were the only symptoms and signs present on admission, making the diagnosis of Meniere's disease almost a certainty. Trigeminal symptoms, although less frequent as initial manifestations, were as frequent in incidence as the auditory complaints. Several cases, in fact, complained mainly of tic douloureux, and with this diagnosis they were operated upon. Cerebellar disturbances and headaches were rare as initial symptoms but occurred later with relative frequency. Headaches were more common in this group than in the cholesteatomas and almost as frequent as in the solitary acoustic neurinomas. Objectively we find more or less the same pattern of findings as in the acoustic neurinomas. The most prominent involvement was that of the auditory nerve, although in a few cases there was no affection of either the cochlear or vestibular component in contradistinction to the neurinomas of the VIIIth N. The Vth N. was affected next in order of frequency. The facial nerve was more commonly affected than in any of the group. Papilledema and cerebellar signs were more frequent than in the pearly body tumors, but as common as in the neurinoma group. Involvement of other cranial nerves, sensory and pyramidal signs were very uncommon. Roentgenologic evidence of erosion at the porus acusticus was infrequent.

The differential diagnosis of these tumors from the acoustic neurinomas may be difficult; in many cases, however, we might make an accurate diagnosis if we remember that the meningiomas occur in a higher age group, that the VIIth N. is more commonly affected, and that radiographic erosion of the porus is quite rare.

GLIOMAS

Gliomas at the recess are less numerous than the previous tumors in spite of the relative frequency of neoplasms of the glial group arising from the cerebellum and brain stem in childhood and adoles-

cence. The locus of origin of these tumors is most likely from either of these two structures, but we could well expect intrinsic gliomas of the acoustic nerve if we bear in mind that the extracannalicular portion of the VIIIth N. is covered mostly by glial tissue (1, 10). The occurrence of these intrinsic tumors is extremely rare and a single report was not found in the literature. One case occurred in this series arising from the VIIIth N.

Twelve gliomas (5.9 per cent) at the cerebellopontile recess were found in this series, and the individual types will be discussed separately as they present interesting characteristics.

1. Astrocytomas

Five cases (2.4 per cent) comprise this group, all females. Three were present on the right and two on the left. No history of trauma or infection could be elicited coincidental to the initial symptoms. The average age of the patients on admission was much younger than in any of the preceding groups of miscellaneous tumors; e.g., 29.4 years, the youngest 7 and the oldest 50. The average age at the onset of symptoms was 26.3 years, the youngest 6½ and the oldest 41. The duration of symptoms was 3.1 years, the shortest 2 months and the longest 9 years.

Symptomatology: The most common subjective disturbances on admission were those referable to the VIIIth N. which were present in all cases. They represented the initial complaint in four. Unilateral diminution of hearing and tinnitus were present together in three and as isolated manifestations in two. Vestibular disturbances on the other hand were conspicuously absent. Cerebellar manifestations were the next most common and followed in every case the symptoms referable to the VIIIth N. This in itself was rather surprising considering that these tumors arise either from the cerebellum or brain stem. Trigeminal symptoms were less common and were present in three cases. They never represented the initial symptom. One patient complained of typical tic douloureux and the other two of subjective numbness of the face on one side. Symptoms referable to the VIth N. were present in three cases, in one of which they represented the initial manifestation. A history of facial weakness was also elicited in three, one of them showing spasmodic contractions of

the facial muscles on the ipsilateral side. The IXth and Xth nerves were subjectively involved in one case. Involvement of the XIth and XIIth nerves was absent. Pyramidal and sensory changes were present contralaterally in one case. Headaches appeared in two cases, generalized in one and bifrontal in the other, and represented the initial symptom in one.

Signs: All patients were conscious, alert, and cooperative on admission. The olfactory nerve was not found involved objectively and vision was good in all cases. There was bitemporal hemianopsia for color in one patient in whom X-ray examination showed enlargement of the sella and destruction of its floor, undoubtedly due to pressure from an enlarged third ventricle. Bilateral papilledema was present in two. No abnormalities of either the IIIrd or IVth cranial nerves could be found. Four cases had ipsilateral absent corneal reflexes and sensory changes on the face. Involvement of the VIth N. was corroborated in three, ipsilateral in two, and contralateral in one.

The VIIth N. was affected in all cases. The facial paralysis was of the peripheral type, partial in four and complete in one. Diminution of hearing was elicited in four patients. No hearing deficit was found in one patient but he complained of tinnitus on admission. It is unfortunate that vestibular tests were performed in only one case with deficient hearing. The caloric response was normal in this case. Involvement of other cranial nerves could not be discovered on examination.

There were bilateral pyramidal signs in one case with contralateral sensory changes. Cerebellar disturbances were constant, being present in all. Unilateral ataxia was uniform, while nystagmus was present in three. The nystagmus was of the horizontal type.

These tumors were fibrillary astrocytomas. Three seemed to arise from the undersurface of the cerebellar lobes, one from the brain stem and another one from the VIIIth N.

Comments: Astrocytomas at the angle producing symptoms similar to acoustic neurinomas are rare and occurred in 2.4 per cent of the cases. Females were selectively affected. The average age at the onset was 26.3 years and the duration of symptoms 3.1 years, these figures being definitely lower than the solitary acoustic neurinomas. There was no definite chronologic order of symptoms. Auditory

manifestations represented the initial disturbance in three, diplopia in one and generalized headaches in another. However, the auditory and cerebellar symptoms were the most frequent. Objectively the only constant signs were those referable to the VIIth N. and cerebellar pathways, the VIIIth and Vth nerves being affected next in order of frequency. No changes were elicited on X-ray of the porus acusticus. These tumors may be differentiated from the solitary acoustic neurinomas by the younger age of the patient, the shorter duration of symptoms, the predominance of VIIth N. and cerebellar signs, and by the absence of x-ray changes of the porus acusticus.

2. Astroblastomas

Just one case of this kind appeared in our series, comprising 0.5 per cent. For purpose of simplification it is summarized immediately.

Case report. F. Q., W. M., 18, Hist. No. U-52914—Admitted on December 27, 1933, with the history that for one year previous to admission he had been complaining of intermittent attacks of projectile vomiting, without nausea, which gradually had become more frequent. Periodic attacks of occipital headaches increased by straining had been present for seven months. Headaches were accompanied by intermittent diplopia. Increasing weakness and clumsiness of the right arm and leg for four months. Marked stiffness of the neck for two weeks. On admission the physical examination was negative. The neurologic examination showed bilateral papilledema with a small hemorrhage in the left disk; horizontal nystagmus; diminished right corneal reflex; diplopia in all fields of vision without definite paresis of E.O.M.; normal hearing but absent vestibular response bilaterally; ataxia of right arm and leg; staggering gait and positive Romberg. X-rays of the skull not taken. Preoperative diagnosis: right cerebellar glioma with possible extension to the angle. Operation (Dec. 28): bilateral cerebellar approach. A large tumor found in the right recess. Tumor apparently arose from the cerebellum pressing tightly against brain stem and slightly attached to it. The VIIth and VIIIth cranial nerves were distorted by the mass. Complete removal by careful dissection. Weight: 17½ gms. Histological diagnosis: astroblastoma. Postoperative convalescence was good.

When last seen, twelve years after the operation, he was perfectly well except for a residual facial paralysis on the right.

Comments: The differential diagnosis in this case would not be difficult if we consider the young age of the patient, the prominence of symptoms of increased intracranial pressure from the onset, the short duration of symptoms, the absence of auditory disturbances, and the predominance of signs referable to the Vth and VIth cranial nerves as well as the cerebellar pathways. Marked papilledema was present. The good result in this case proves that it is always worthwhile to attempt a complete removal of gliomas at the angle.

3. Medulloblastoma

This group is comprised of three cases (1.5 per cent). One female and two males were affected. In one the symptoms were coincidental with trauma to the head on the affected side. The right side was invariably involved. The average age of the patients on admission was 30.6 years, the youngest 23 and the oldest 38. The average age at the onset was 28.1 years, the youngest 21 and the oldest 33, and the duration of symptoms was 2.5 years, the shortest 5 months and the longest 5 years. Auditory disturbances, peripheral facial weakness and cerebellar manifestations represented the initial symptoms in these three cases respectively. Symptoms referable to the VIIIth N. were present in all cases: bilateral tinnitus present in one and unilateral deafness in two. There were no vestibular disturbances. Cerebellar manifestations and subjective involvement of the Vth and VIIth nerves occurred in two cases. Headaches were a late symptom and were present in two. Dysarthria was present in one case. There was no subjective involvement of the pyramidal or sensory tracts.

Signs: The patients were conscious and alert on admission. Anosmia was not elicited in any of the cases. Disturbances to the Vth and VIIIth nerves as well as unilateral cerebellar signs were present in all. The corneal reflex was absent in two, and sensory changes on the face were elicited in each case. There were no abnormalities of the extra-ocular movements. Facial paralysis was present in two, being partial and complete in each case respectively. Unilateral nerve deafness was uniformly present. Caloric tests were performed in one case and showed absent vestibular response on the same side

as the defective hearing. Unilaterial ataxia and nystagmus were present in every case There were no pyramidal or sensory changes in the body or extremities. X-rays of the skull were reported as negative in all the cases.

At operation typical medulloblastomas were found arising from either the brain stem or cerebellum. All patients were discharged in an improved condition, but adequate follow-up studies were carried in only one case who died 5 years after the operation with massive recurrence.

Comments: Medulloblastomas are essentailly tumors of childhood. It is surprising that the only three cases found in these series occurred at a much later age; e.g., 28.1 years. On the other hand it is also surprising that in these rapidly growing neoplasms the average duration of symptoms was 2.5 years. These figures correspond closely to the astrocytoma series and are much lower than the unilateral acoustic neurinomas. Although auditory involvement was a constant sign it represented the initial symptom in only one case. Vth N. and cerebellar signs were likewise present in all three cases. Papilledema was uniformly absent. No X-ray changes were found. No definite conclusions can be drawn from this small group of cases but these tumors apparently may be differentiated from the acoustic neurinomas by the earlier age of onset, the shorter duration of symptoms, the low incidence or absence of papilledema and the lack of changes at the porus as evidenced by X-ray examination.

4. Ependymomas

Two cases (0.9 per cent) occurred in this group, both of them being in males 37 and 48 years of age on admission. The average age at the onset of symptoms was 40 years with a duration of 2.5 years. The right and the left side were respectively affected. Diminution of hearing and numbness of the face were the initial symptomatology in one, while severe generalized headaches represented the first manifestations in the other. Dysphagia, dysarthria and cerebellar disturbances were present in both, occurring as late manifestations. There was history of intermittent contraction of the face in one.

Signs: On admission both patients were alert and cooperative with no impairment of vision and no papilledema. Unilateral involvement

of the Vth, VIIth, VIIIth, IXth and Xth cranial nerves was present in both cases, as well as unilateral cerebellar signs. Horizontal nystagmus could only be elicited in one. Vestibular tests were performed on one who showed no response on either side. X-rays of the skull were normal in one while the other showed erosion of the porus acusticus.

At operation typical ependymomas were found at the angle extending from the fourth ventricle into the recess. One patient is living and well at the end of one and a half years. No follow-up studies were carried on in the other.

Comments: The age of these two cases falls approximately in the same group as the unilateral acoustic neurinomas, but the duration of symptoms was much shorter. In one the diagnosis of an acoustic neurinoma could have been easily ruled out as auditory disturbances were a late manifestation. Another differential point from the acoustic neurinomas in both cases was the absence of papilledema in the presence of such marked involvement of the cranial nerves.

5. *Glioblastoma multiforme*

They were extremely rare in this series which is not surprising if we consider that they are primarily tumors of the cerebral hemispheres. Only one case (0.5 per cent) was found.

Case report: J. F. K., W. M., 37, Hist. No. 11874—Admitted Apr. 30, 1927, with the history that for four years he had been suffering from gradual diminution of hearing on the right which became complete in six months. One year after the onset of hearing difficulties he had paralysis of the right side of the face which was complete in a few days and subsequently remained unchanged. For two and a half years there had been intermittent headaches at the vertex accompanied by dizziness whenever he moved his head. Gradual blurring of vision for one year. On admission the physical examination was negative. The neurologic examination revealed bilateral papilledema; horizontal nystagmus; absent right corneal reflex and hypesthesia of right face; complete peripheral VIIth N. paralysis; complete right nerve deafness; absent vestibular response on the right; dysmetria and asynergia in right arm and leg and a positive Romberg. X-rays of the skull not reported. Operation: (May 5): bilateral cerebellar ap-

proach. Ventricles were large and fluid spurted under considerable pressure. A large tumor was found at the right recess invading the spinal canal. It was slightly attached to the brain stem from which it was dissected. The tumor appeared to be attached to the dura and indented the internal auditory meatus. It was completely removed. Weight: 39 gms. Histological diagnosis: glioblastoma multiforme. Postoperative convalescence was good and the patient was discharged on the 24th postoperative day. No follow-up.

Comment: It is inconceivable that a tumor of this kind should have a history of four years' duration although it might have represented in its incipient stage one of the more benign gliomas which underwent malignant changes later. Clinically it was difficult to distinguish from the unilateral acoustic neurinomas except for the earlier age at the onset of symptoms and by the fact that the facial paralysis was complete. This case proves how futile at times a clinical differentiation may be.

ABSCESSES

As mentioned above, abscesses, although inflammatory in nature, may behave like any tumor at the recess and therefore must be considered in the differential diagnosis. Four such cases (2 per cent) comprise this group. Two of them were metastatic, secondary to a pyogenic focus elsewhere in the body, while the other two were direct sequelae of a middle ear infection. Three males and one female were affected. The right and left sides were involved in an equal number of cases.

In the otogenic abscesses symptoms appeared one week and nine years respectively after the onset of the primary infection. In cases where the primary source was remote, e.g., osteomyelitis of the femur, the onset of symptoms started 6 and 15 months respectively after the original infection. The average duration of symptoms in three was three weeks, while in the other was four years. The average age on admission was 17.5 years, the youngest 11 and the oldest 22. The age at the appearance of symptoms was 16.1 years, the youngest 10 and the oldest 21.5. Facial paralysis was the initial symptom in two, unilateral diminution of hearing in one, and generalized headaches in another. Cerebellar manifestations were present in two, appearing

late in the course of the disease. There was no subjective involvement of the Vth N. in any of the cases. Unilateral diminution of hearing was present in one case and diplopia in another. Otherwise subjective manifestations of cranial nerve involvement were rare.

Signs: Only one case was drowsy on admission; the others were alert and cooperative. Varying elevation of temperature was present in three with moderate leucocytosis. Bilateral papilledema with hemorrhages and exudates was found in three and bilateral IIIrd N. palsy in one. Unilateral absence of the corneal reflex was elicited in one and bilaterally in another. No sensory changes on the face could be demonstrated. Paralysis of the VIth N. occurred in one case on the same side as the lesion. Peripheral facial paralysis was the most constant sign. It was found in all, complete in two and incomplete in the remainder. Hearing was absent in two with total loss of vestibular response. The left vocal cord was affected in one. Pyramidal signs were present in two, always contralateral to the lesion. Cerebellar signs were as common as the VIIth N. involvement occurring in all. The ataxia was unilateral and on the same side as the lesion. Nystagmus appeared in two cases.

X-rays of the skull were uniformly negative.

At operation the unilateral cerebellar approach was used in two and the bilateral in the others. Only the patients in whom the bilateral approach was used survived and are still living one and four and a half years respectively after the operation. In two the offending organism was Staphylococcus aureus, in one Staphylococcus albus hemolyticus, and no cultures were reported in the other.

Comments: Four cases with abscesses at the cerebellopontile recess have been analyzed. In one case the diagnosis of acoustic neurinomas was made due to the long duration of symptoms and to the predominance of the auditory disturbances, although another lesion should have been suspected if the early age of onset had been considered. In the other three the diagnosis of an abscess at the angle was suspected due to the early age of the patients, the short duration of symptoms, the febrile condition with leucocytosis and the unilateral neurologic signs. In all cases a primary pyogenic focus was found either in the middle ear or was an osteomyelitic process in the long bones. Therefore, a young patient with a focus of infection in the

body presenting unilateral cranial nerves and cerebellar involvement should be regarded potentially as harboring an abscess at the cerebellopontile recess.

How infection finds its way into the angle has been explained by others (6). In the otogenic abscesses two avenues of spread have been described: 1. osteomyelitis of the petrous tip, and 2. by local extension through the internal auditory canal. Thus a Gradenigo's syndrome may precede the symptoms of a lesion at the recess.

When the abscess is secondary to a remote infection, it must be metastatic, the metastases taking place in all probability to a cerebellar lobe from which it invades the angle or ruptures into it producing a localized collection of pus surrounded by dense fibrous adhesions.

MISCELLANEOUS TUMORS

This group is comprised of three cases: a sarcoma of the meninges, a carotid body tumor, and a malignant melanoma which are summarized below.

1. Sarcoma of the meninges

Case report. A. R., W. M., 11, Hist. No. 356553—Admitted July 6, 1945, with the history that nine months before admission he had a sudden paralysis of the right side of the face which was diagnosed as a Bell's palsy. One and one-half months later almost constant attacks of rotary vertigo, bifrontal headaches, nausea and vomiting and some staggering on walking appeared. The diagnosis of right otitis media and mastoiditis was made elsewhere and a simple mastoidectomy on the right performed, followed by a simple mastoidectomy on the left one month afterward. Following these operations the vertigo disappeared, but the headaches and vomiting persisted with subsequent loss in weight. One month before admission he developed a bilateral convergent squint and the staggering became worse and more pronounced to the right. Vomiting had been almost continuous for a week. On admission the physical examination showed a chronically ill boy with a normal temperature and white cell count. There was no evidence of chronic ear infection A marked laceration of the right cornea was found. The neurologic examination showed moderate engorgement of the retinal veins; bilateral VIth N. paralysis, complete

on the right and partial on the left; absent right corneal reflex; analgesia and anaesthesia on the whole right side of the face; marked weakness of the right masseters and pterygoids; complete right peripheral facial paralysis with loss of taste on the anterior two-thirds of the tongue; neurogenic type of deafness on the right; paralysis of the right palate, and marked ataxia on the right. X-rays of the skull showed a destructive process involving the right petrous ridge, extending along the middle fossa, obliterating the foramina in the base and extending as far forward as the posterior border of the anterior fossa. First operation (July 7): right cerebellar approach. Resection of the cerebellar cap. A large, reddish, extremely hard tumor was found at the recess which was considered inoperable and no attempt was made to remove it. Postoperatively patient's condition was worse with increasing drowsiness and three days later it was decided to make an attempt to remove the neoplasm. Second operation (July 10): The wound was reopened. The tumor had made a tremendous erosion at the porus and could not be shelled from the base even after liberating the margins. A large part of the tumor was cut away with the knife and scissors. Postoperatively the child never regained consciousness and died twenty-four hours after. Permission for necropsy was not granted. Histological diagnosis of the tumor: sarcoma of the meninges.

Comments: It was obvious from the history of the patient that this did not represent an acoustic neurinoma. His age, the early appearance of symptoms of increased intracranial pressure, the complete facial paralysis and the rapid progression of symptoms made the diagnosis of a neurinoma quite improbable. The possibility of an abscess at the recess was considered but was discarded in the presence of such marked erosion of the base of the skull which made the diagnosis of a highly malignant lesion, possibly an osteogenic sarcoma, the most likely.

2. *Carotid body tumor (perithelioma of the carotid gland)*

Although there are several instances in the literature of tumors arising from the carotid gland invading and eroding the skull, a single case was not encountered where this kind of neoplasm was found within the cranium without demonstrable signs of its presence

in the neck. The following case is an example of such an occurrence which is reported in detail because of its rareness.

Case report. W. B., W. M., 38, Hist. No. U-7229—Admitted Aug. 30, 1926, with the history that twelve years previously he had developed sudden hoarseness with slight dysphagia which had since remained unchanged. Two years later, following an attack of influenza, he became deaf on the right. The tympanic membrane was punctured at that time, and following this an intermittent, chronic discharge had been present. He had had for eight years periodic attacks of vertigo (? rotary) accompanied at times by staggering to the right. These attacks occurred in the beginning about twice a month, but for one year previous to admission they occurred from two to three times a week, followed at times by profound unconsciousness lasting for one hour. Persistent diplopia for eight months. Severe suboccipital headaches which had been almost constant, accompanied by marked exacerbations of vertigo, at times so severe as to keep him awake most of the night, had been present for four weeks. Two days before admission he became increasingly drowsy. On admission the physical examination was essentially negative. No masses were palpable in the neck and there were no visible pulsations. The neurologic examination showed bilateral papilledema of 1 D., more pronounced on the right; complete right VIth N. paralysis; complete neurogenic deafness on the right with absence of vestibular response on the same side; paralysis of the right palate and vocal cord; marked atrophy and paralysis of right sternomastoid and trapezius; atrophy of right side of the tongue and slight dysmetria and asynergia of the right arm. X-rays of the skull showed an enlarged sella turcica but no data was given as to views of the base. Preoperative diagnosis: cerebellopontile angle tumor. Operation (Sept. 4): bilateral cerebellar approach. A big tumor found in the right recess. There was furious bleeding from the tentorial veins on retracting the cerebellum, so much in fact that a quick enucleation of the tumor with the finger was attempted. Enucleation was difficult. The tumor had eroded the base of the skull and apparently invaded the deep muscles of the neck and extended into the lateral sinus. Uncontrollable, exsanguinating hemorrhage occurred and the patient died on the operating table. Autopsy was obtained but unfortunately was limited to the head.

Autopsy findings: There was a ragged hole about 2–3 cm. in diameter in the base on the skull at about the position of the jugular foramen on the right and mushy-looking tissue could be seen projecting from it. Some of the tissue in the neck was removed through the hole in the skull, but it looked like normal muscle. Between cerebellum and medulla on the right there was a gouged-out cavity from which a tumor had been removed. On section the aqueduct was compressed and distorted but not occluded. No evidence of tumor was seen invading the brain stem or cerebellum. Microscopic examination: "Tumor has a framework which divides it up into rather small areas which are somewhat rounded and apparently surrounded by a continuous cleft. There are channels like blood vessels running through such areas. They have rather thick walls and not very conspicuous endothelium. The remainder of such areas is made up of strands of small masses of quite large cells with vesicular nuclei which do not stain very deeply, and with a finely granular cytoplasm suggesting the presence of fat. In sections of tissue from the neck the tumor is found in a large vein. No tumor tissue can be seen in the lymph glands." Diagnosis: carotid body tumor.

Comment: This case might have been diagnosed as a neurinoma arising from the Xth N. if the initial symptoms of hoarseness and dysphagia had been considered. The prolonged duration of symptoms without earlier signs of increased intracranial pressure makes this diagnosis somewhat doubtful. The diagnosis of a carotid body tumor with invasion of the angle could not have been made in the absence of a palpable mass in the neck. The site of origin of this tumor can be only a matter of conjecture, the most plausible explanation is that it originally arose from displaced fragments of chromaffin cells in or in the neighborhood of the jugular foramen, producing early unilateral pressure on the glossopharyngeal and vagus nerves. The slow growth into the cranium explains the late appearance of other neurologic manifestations.

3. Malignant melanoma

Case report. J. B., W. M., 62, Hist. No. 130428—Admitted Feb. 14, 1938, with the history that four months previously he had developed pronounced numbness in the left hand which lasted for three weeks

and reappeared three weeks before admission. Diplopia, sudden loss of hearing on the right, dizziness in change of position of the head, and staggering to the right on walking had been present for four weeks. No headaches. On admission the physical examination was negative. The neurological examination showed a rhythmical horizontal nystagmus; weakness of the left side of the face, peripheral in type; total nerve deafness, right; absence of vestibular response on the right; ataxia of the right arm and astereognosis in left hand. Operation (Feb. 15): ventricular air injection performed: Ventricles were normal. Unilateral cerebellar exploration performed on the right side. At the recess a dark reddish-brown tumor extending from the VIIIth to the Xth N. was seen and did not seem to infiltrate either the cerebellum or brain stem. Tumor was shelled out completely. Weight: 3.4 gms. Histological diagnosis: metastatic malignant melanoma. The patient was discharged in apparently good condition, but died suddenly at home three months after operation. No autopsy performed.

Comments: The rapidity of symptom in quite an elderly individual should have made the diagnosis of a metastatic lesion at the cerebellopontile recess quite obvious, even in the absence of clinical evidence of a primary source. The sensory changes in the left hand in the absence of evidence of pressure of the tumor on the brain stem at operation point to a small metastasis in the right parietal lobe in spite of the normal air studies. The late appearance of hearing difficulties would exclude a tumor arising from the VIIIth N.

CONCLUSIONS

1. The age of onset and duration of symptoms are the most important points in the differential diagnosis of tumors at the cerebellopontile recess.

2. In the first two decades of life we have shown that the most common tumors are the unilateral acoustic neurinomas with peripheral neurofibromatosis, the bilateral acoustic neurinomas and abscesses. The average duration of symptoms of ten, five and one years respectively help in their differential diagnosis.

3. Gliomas at the recess occur predominantly between twenty and thirty years of age with a duration of symptoms varying from one to three years.

4. Between thirty and forty years of age the unilateral acoustic neurinomas, without peripheral neurofibromatosis, and the cholesteatomas are most commonly found. The former occur in the late 30's with an average duration of symptoms of four and a half years, while the latter start to manifest themselves in the early 30's with an average duration of symptoms of seven years.

5. The meningiomas have the same average duration of symptoms as the unilateral acoustic neurinomas but they appear mostly between forty and fifty years of age.

6. After the age of fifty, tumors at the cerebellopontile recess are uncommon.

7. There is no specificity in chronology of symptoms. Perhaps the only differential point is that most cases of acoustic neurinomas initiate their symptoms with auditory and/or labyrinthine disturbances, but we have seen that this is also true, although in a lesser degree, of the meningiomas and gliomas.

8. When the initial symptom is characterized by tic douloureux or other symptoms referable to the Vth N. we should suspect either a cholesteatoma or a neurinoma arising from the Vth N.

9. The neurologic examination shows the same variation in signs in different tumors at the recess except in the cholesteatomas in which VIIIth N. involvement is rare while involvement of the Vth N. is quite common.

10. When X-rays of the base of the skull show erosion of the porus acusticus we must conclude that we are dealing with an acoustic neurinoma, as it is present in fifty per cent of these tumors and rarely in the rest.

SUMMARY

1. Two hundred and five cases of tumors of the cerebellopontile recess, verified at operation at The Johns Hopkins Hospital in a period of twenty years, have been analyzed.

2. Their main differential characteristics have been discussed.

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EFFECT OF PARA-AMINOHIPPURIC ACID ON SODIUM THIOSULFATE DETERMINATIONS IN RENAL CLEARANCE STUDIES

STUART R. ELLIOTT, II, AND H. WILLIAM SCOTT, JR.

From the Department of Surgery of the Johns Hopkins University and Hospital, Baltimore, Md.

Received for publication March 6, 1948

In beginning a study of the renal blood flow in patients with congenital cyanotic heart disease, the clearance of para-aminohippuric acid was used for the determination of effective renal plasma flow and the functional capacity of the tubular excretory system (1). Sodium thiosulfate clearance was employed to measure glomerular filtration. Thiosulfate clearance has recently been established as an accurate estimate of glomerular filtration by Gilman, Newman and co-workers (2, 3). Its advantage over inulin and mannitol clearances lies in the ease and accuracy of the chemical determination of thiosulfate. Simultaneous clearances of para-aminohippuric acid (PAH) and sodium thiosulfate were carried out according to the general technique outlined by Homer Smith and associates (1).

It was noted in these clearances that the determination of sodium thiosulfate in serum filtrates containing high concentrations of PAH gave unsatisfactory checks in duplicate aliquots. Satisfactory checks were obtained with low concentrations of PAH and in serum blanks containing no PAH.

It was also observed that the second thiosulfate determination in duplicate aliquots of the filtrates containing excessive PAH gave a value consistently higher than the first. The only variant in the determination of the duplicates was the length of time of acidification before titration.

These observations prompted an investigation of the effects of (1) varying concentrations of PAH, and (2) varying time intervals of acidification, on sodium thiosulfate titration values in aqueous, serum and plasma solutions of known concentration.

METHODS

Para-aminohippuric acid was determined by the method of Smith, Finkelstein, Aliminosa, Crawford and Graber (1). Sodium thiosulfate was determined by the "indirect" method recommended by Newman, Gilman and Philips (3) for the low thiosulfate levels found in serum. In this procedure proteins are precipitated with sodium tungstate and sulphuric acid. After centrifugation a 10 ml. aliquot of the supernatant fluid is added to 10 ml. of 0.01 normal potassium iodate solution and acidified with 2 ml. of 2 normal hydrochloric acid. The mixture is allowed to stand for at least five minutes. Then 2 ml. of freshly prepared 10 per cent potassium iodide are added. The liberated iodine is immediately titrated with 0.01 normal sodium thiosulfate, with the addition of a few drops of 1 per cent fresh starch solution as indicator when the iodine color fades. According to Newman et al. (3) the reactions involved are the following:

$$2KIO_3 + Na_2S_2O_3 + 2HCl = Na_2SO_4 + K_2SO_4 + H_2O + 2ICl$$

$$2KI + 2ICl = 2I_2 + 2KCl$$

$$2KIO_3 + 10KI + 12HCl = 6I_2 + 12KCl + 6H_2O$$

$$2Na_2S_2O_3 + I_2 = Na_2S_4O_6 + 2NaI$$

The formula for the calculation of concentration in milligrams per cent is:

$$\text{Standardizing titration} - \text{unknown titration} \times \frac{1.58}{8} \times \frac{10}{\text{Standardizing titr.}} \times \frac{100 \times 10}{\text{cc. of filtrate aliquot used}}$$

PREPARATION OF SOLUTIONS

In this series of experiments a stock 100 mg. per cent sodium thiosulfate solution (156.9 mg. $Na_2S_2O_3 \cdot 5H_2O$ and 10 mg. Na_2CO_3 dissolved in 100 ml. distilled water) and a stock 750 mg. per cent para-aminohippuric acid solution (375 mg. para-aminohippuric acid dissolved in 50 ml. distilled water with the aid of sodium carbonate) were prepared.

In the plasma and serum experiments two variations were employed. In the first, 35 ml. of serum or citrated plasma and 10 ml. of the 100 mg. per cent sodium thiosulfate solution were mixed with either 5 ml. of the 750 mg. per cent para-

aminohippuric acid solution, 5 ml. of some dilution of this solution, or with 5 ml. of distilled water in 50 ml. volumetric flasks. Serum or citrated plasma blanks consisted of 35 ml. of serum or citrated plasma and 15 ml. distilled water. To an aliquot of these stock serum or citrated plasma solutions was added seven volumes of water, one volume of 5 per cent sodium tungstate solution and one volume of one-third normal sulphuric acid solution. After centrifugation and filtration, aliquots were used for sodium thiosulfate determinations. In another aliquot of the stock serum or citrated plasma proteins were precipitated with acid cadmium sulfate and sodium hydroxide solutions and the filtrate was used to estimate the PAH level. In the second variation suitable portions of dilutions of the stock solutions were added to serum and oxalated plasma, whose protein was then precipitated with sodium tungstate and sulphuric acid solutions as above. Thus in both cases sodium thiosulfate and PAH were present at the time of protein precipitation and were not added afterwards.

In the case of aqueous solutions, 10 ml. of the 100 mg. per cent sodium thiosulfate solution were diluted to 50 ml. in a volumetric flask and 25 ml. of this were diluted to 250 ml.; or 5 ml. of the stock 100 mg. per cent sodium thiosulfate solution were diluted directly to 250 ml. in a volumetric flask. PAH was either added before diluting by using a suitable quantity of the stock solution or the necessary amount of powder was weighed out and dissolved in the diluted sodium thiosulfate.

The 0.01 N potassium iodate solution was obtained by diluting the 0.1 N stock solution (3.567 grams potassium iodate dissolved in one liter distilled water) tenfold on the day of use. The 10 per cent potassium iodide solution was prepared in small amounts, was kept in a brown bottle in an ice bath and was used not longer than one hour after preparation. The starch solution was prepared freshly each day and was centrifuged before use. The sodium thiosulfate solution used for the titration of the liberated iodine was made more than 0.01 N and its true concentration was determined with the 0.01 N potassium iodate. A 10 ml. micro burette, graduated to fiftieths of a milliliter, was employed and readings were made to hundredths of a milliliter. All titrations were performed at room temperature in the absence of direct sunlight. An interval timer was used to measure the time between the addition of the acid and of the potassium iodide which was immediately followed by titration of the liberated iodine.

EXPERIMENTAL PROCEDURES AND RESULTS

Control experiments were set up which used water, serum and plasma solutions of sodium thiosulfate in a concentration of 20 mg. per cent. This level represents the desirable range of thiosulfate concentration for the measurement of glomerular filtration rate in man (4). Equivalent solutions of sodium thiosulfate were prepared containing low, intermediate and high concentrations of PAH. Titrations in duplicate (occasionally in triplicate) of sodium thiosulfate in filtrates of these

solutions were then performed after intervals between acidification and titration of 1, 2, 3, 5, 15, 30 and 60 minutes. Correction was made for the serum or plasma blank titration in each instance (3).

A few experiments were conducted along exactly similar lines with sodium thiosulfate in 40 and 60 mg. per cent concentration.

The results of these experimental determinations are presented in Table I in summary form. For each set of observations there is presented the average determination, the range and the number of determinations. In 105 determinations of the aqueous controls (20 mg. per cent sodium thiosulfate solutions containing no PAH) the average is 19.90 mg. per cent with a range of 19.3 to 20.7 mg. per cent. The average for the aqueous 40 mg. per cent sodium thiosulfate control containing no PAH (20 determinations) is 39.77 mg. per cent with a range of 39.4 to 40.4 mg. per cent. The average for the aqueous 60 mg. per cent sodium thiosulfate controls containing no PAH (18 determinations) is 59.32 mg. per cent with a range of 58.8 to 60.0 mg. per cent.

It will be assumed that if the average of a set of determinations falls outside of a range of two per cent greater to two per cent less than the respective control average, there is a significant difference between that set and the control set. For 20 mg. per cent sodium thiosulfate this range is 19.5 to 20.3 mg. per cent; for 40 mg. per cent, 39.0 to 40.6 mg. per cent; for 60 mg. per cent, 58.1 to 60.5 mg. per cent.

In Figure 1 the effect of high and low concentrations of PAH on 20 mg. per cent sodium thiosulfate determinations is plotted as a function of the time between acidification and titration. From the graph it is seen that in the presence of high concentrations of PAH the apparent sodium thiosulfate levels increase rapidly with time. This occurs in water, serum and plasma solutions. With low concentrations of PAH this increase in apparent sodium thiosulfate levels is manifested to a limited extent in plasma solutions but is not observed in serum and water solutions. The use of plasma is not recommended, since oxalate and citrate appear to augment the false elevation.

Essentially the same results are obtained with 40 and 60 mg. per cent sodium thiosulfate in aqueous and serum solutions containing high concentrations of PAH.

The false elevation of aqueous sodium thiosulfate levels increases slightly with increased sodium thiosulfate concentration when the

TABLE I

The effect of varying the concentration of para-aminohippuric acid and varying the interval between acidification and titration on the calculated concentration of sodium thiosulfate

TRUE MG. % SODIUM THIOSULFATE	MG. % PAH	MEDIA	CALCULATED MG. PER CENT SODIUM THIOSULFATE USING VARYING INTERVALS BETWEEN ACIDIFICATION AND TITRATION							
			1 min.	2 min.	3 min.	5 min.	15 min.	30 min.	60 min.	
20.0	0	Water	19.88	19.78	19.92	19.85	20.05	19.88	19.98	Aver.
			20.7	20.2	20.5	20.4	20.2	20.2	20.2	Max.
			19.4	19.5	19.3	19.4	19.7	19.6	19.5	Min.
			(24)	(5)	(13)	(28)	(12)	(11)	(12)	N
20.0	2.18 2.76 4.11	Water	20.17		20.03	19.83	20.06	20.59	20.56	Aver.
			20.6		20.4	20.2	20.6	22.0	21.2	Max.
			19.8		19.7	19.5	19.4	19.8	19.6	Min.
			(6)		(6)	(6)	(6)	(7)	(8)	N
20.0	75* 75* 75*	Water	20.28		21.20	22.09	23.83	26.15	28.13	Aver.
			20.7		21.6	22.6	24.4	26.8	29.4	Max.
			19.5		20.7	21.6	23.2	25.4	27.0	Min.
			(6)		(6)	(7)	(6)	(6)	(6)	N
20.0	0	Plasma	19.70		*20.03*	20.26	20.27	20.53†	20.73†	Aver.
			20.6		20.6	20.8	21.1	21.1	21.5	Max.
			19.0		19.3	19.7	19.8	20.1	19.9	Min.
			(6)		(6)	(8)	(6)	(6)	(6)	N
20.0	2.27 2.85	Plasma	19.38		*20.20*	20.97	20.50	21.30†	21.65†	Aver.
			20.0		20.6	21.4	21.3	21.9	22.5	Max.
			18.8		19.6	20.6	19.6	20.7	20.9	Min.
			(4)		(4)	(6)	(4)	(4)	(4)	N
20.0	69.5 74.0 75*	Plasma	*19.97*		21.72	22.26	24.67	27.67†	29.48†	Aver.
			20.5		23.0	22.6	25.7	28.1	30.4	Max.
			19.0		20.9	21.5	23.5	26.1	28.0	Min.
			(6)		(6)	(8)	(6)	(6)	(6)	N
20.0	0	Serum	19.22	19.52	19.20	*19.98*	19.70	19.60	19.90	Aver.
			19.8	20.0	19.3	20.4	19.9	19.7	19.9	Max.
			18.3	19.2	19.1	19.2	19.5	19.5	19.9	Min.
			(9)	(5)	(3)	(9)	(2)	(2)	(2)	N

TABLE I—*Continued*

TRUE MG. % SODIUM THIO-SULFATE	MG. % PAH	MEDI	CALCULATED MG. PER CENT SODIUM THIOSULFATE USING VARYING INTERVALS BETWEEN ACIDIFICATION AND TITRATION							
			1 min.	2 min.	3 min.	5 min.	15 min.	30 min.	60 min.	
20.0	2.41 2.94 2.96 3.02	Serum	19.15 19.6 18.4 (12)	19.46 19.8 19.2 (7)	19.53 20.0 19.1 (6)	*19.90* 20.8 19.2 (12)	19.80 20.0 19.7 (4)	20.00 20.2 19.9 (4)	20.60 20.7 20.3 (4)	Aver. Max. Min. N
20.0	72.2 73.1 73.6	Serum	*19.69* 20.0 19.2 (9)	20.24 20.8 19.8 (5)	20.43 20.5 20.3 (3)	22.12 22.8 20.9 (9)	23.70 23.9 23.5 (2)	25.40 25.5 25.3 (2)	27.70 28.1 27.3 (2)	Aver. Max. Min. N
40.0	0	Water	39.64 40.2 39.4 (5)	39.60 39.8 39.4 (2)	39.8 (1)	39.92 40.4 39.5 (6)		39.4 (1)	39.84 40.4 39.4 (5)	Aver. Max. Min. N
40.0	73.2 75* 75*	Water	39.74 40.2 39.2 (7)	40.37 40.6 40.0 (6)	41.61 42.5 41.0 (7)	42.59 43.3 41.8 (9)	47.22 47.6 46.7 (6)	50.08 50.6 49.2 (6)	51.64 53.9 46.3 (7)	Aver. Max. Min. N
40.0	0	Serum	39.53 39.6 39.4 (3)	39.87 40.0 39.8 (3)	40.30 40.4 40.2 (2)	*40.50* 41.4 40.2 (6)	38.7 (1)	39.5 (1)	40.3 (1)	Aver. Max. Min. N
40.0	75*	Serum	*40.20* 40.6 39.8 (3)	41.47 42.0 41.2 (3)	42.10 42.2 42.0 (2)	43.50 43.5 43.5 (2)	49.7 (1)	51.3 (1)	56.10 56.4 55.8 (2)	Aver. Max. Min.
60.0	0	Water	59.27 59.6 58.8 (3)	59.40 59.8 59.2 (3)	59.40 59.6 59.0 (3)	59.47 60.0 58.8 (3)	59.20 59.2 59.2 (2)	59.30 59.6 59.0 (2)	59.10 59.4 58.8 (2)	Aver. Max. Min. N

TABLE I—*Concluded*

TRUE MG. % SODIUM THIOSULFATE	MG. % PAH	MEDIA	CALCULATED MG. PER CENT SODIUM THIOSULFATE USING VARYING INTERVALS BETWEEN ACIDIFICATION AND TITRATION							
			1 min.	2 min.	3 min.	5 min.	15 min.	30 min.	60 min.	
60.0	75*	Water	59.87	60.47	61.00	62.47	67.90	72.10	76.90	Aver.
			60.0	60.8	61.2	62.8	68.2	72.2	77.6	Max.
			59.8	60.2	60.6	62.0	67.6	72.0	76.2	Min.
			(3)	(3)	(3)	(3)	(2)	(2)	(2)	N
60.0	0	Serum	59.60	59.93	60.30	*60.47*	59.5	60.1	60.5	Aver.
			60.4	60.2	60.6	60.8				Max.
			58.9	59.6	60.0	60.0				Min.
			(3)	(3)	(2)	(6)	(1)	(1)	(1)	
60.0	75*	Serum	*60.20*	61.47	62.90	64.70	69.0	74.5	80.00	Aver.
			60.6	61.8	63.0	64.8			80.1	Max.
			60.0	61.2	62.8	64.6			79.9	Min.
			(3)	(3)	(2)	(2)	(1)	(1)	(2)	N

Aver. = average; Max. = maximum; Min. = minimum; N = number of determinations; Min. = minute(s).

* Weighed. All other concentrations were determined colorimetrically.

† Opalescent when titrated.

PAH concentration is maintained at 75 mg. per cent. However when the sodium thiosulfate concentration is maintained at 20 mg. per cent while the PAH concentration is varied, the false elevation is nearly proportional to the PAH concentration in the range of 35 to 75 mg. per cent. This false elevation amounts to 0.03 mg. per cent sodium thiosulfate for each mg. per cent PAH present in the undiluted material.

An attempt was made to determine the minimal concentration of PAH required to produce a false elevation of the aqueous 20 mg. per cent sodium thiosulfate level. The false elevation was equivocal at 25 mg. per cent PAH but was definite at 35 mg. per cent PAH using a 5 minute interval between acidification and titration.

COMMENT

Since the false elevation of the sodium thiosulfate level in the presence of high concentrations of PAH increases with the time that

elapses between the addition of acid (reaction I above) and the addition of potassium iodide (reactions II and III above), a reaction must occur between PAH and either potassium iodate, iodine monochloride or both. Regardless of the specific nature of the reaction, it gives rise to a decreased amount of liberated iodine and therefore a decrease in the amount of sodium thiosulfate required for titration, thus indicating an incorrectly high concentration of sodium thiosulfate.

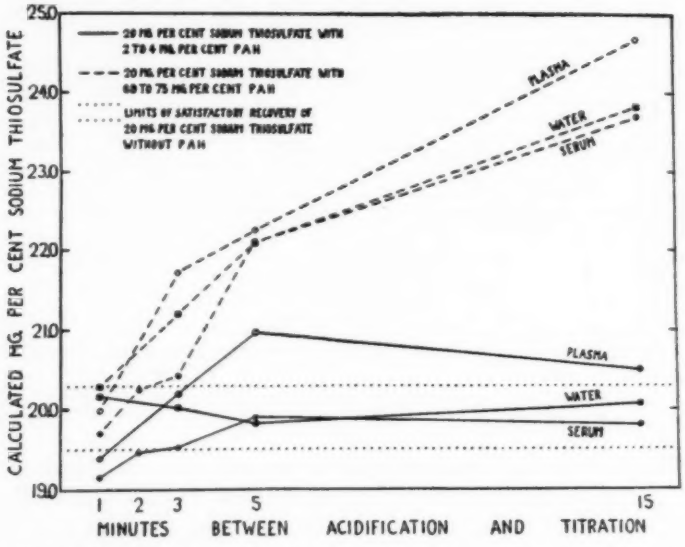
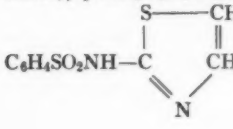


FIG. 1. THE EFFECT OF HIGH AND LOW CONCENTRATIONS OF PAH ON SODIUM THIOSULFATE DETERMINATIONS PLOTTED AS A FUNCTION OF TIME BETWEEN ACIDIFICATION AND TITRATION

In addition to para-aminohippuric acid, p-$NH_2C_6H_4CONHCH_2COOH$, several chemically similar compounds at approximately the same concentration produce a similar false elevation of the sodium thiosulfate level when the latter is measured by this method. These compounds include aniline hydrochloride, $C_6H_5NH_2 \cdot HCl$; para-aminobenzoic acid, p-$NH_2C_6H_4COOH$; para-aminobenzenesulfonic acid (sulfanilic acid), p-$NH_2C_6H_4SO_3H$; para-aminobenzenesulfonamide (sulfanilamide), p-$NH_2C_6H_4SO_2NH_2$; 2-sulfanilyl aminothiazole (sulfathiazole), p-NH_2-

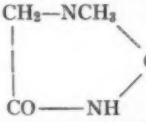


$C_6H_4SO_2NH$—C CH; as well as phenol, C_6H_5OH, and p-hydroxyphenyla-

N

lanine (tyrosine), p-$HOC_6H_4CH_2CH(NH_2)COOH$. When one of these aromatic compounds at the same concentration is subjected to the entire procedure in the absence of sodium thiosulfate, a titration value identical with that of acidified potassium iodate alone is obtained, even if a sixty minute interval between acidification and titration is employed. This would indicate that the side reaction is not oxidation by potassium iodate, but rather some reaction involving iodine monochloride which is produced when sodium thiosulfate is present. In the case of phenol and tyrosine halogenation of the ring, analagous to bromination of phenol, is the most likely reaction. Nascent iodine reacts slowly with PAH. However, halogenation of the ring is probably not the reaction in the case of the amines because both acetanilide, $CH_3CONHC_6H_5$, and para-acetylaminohippuric acid, p-$CH_3CONHC_6H_4CONHCH_2COOH$, cause no false elevation of the thiosulfate levels although both compounds should halogenate. Similarly the substitution of chlorine for one of the hydrogens attached to the amine nitrogen group should not be prevented by acetylation of the amine. However, if the reaction is oxidation of the amine by iodine monochloride, acetylation should prevent this, just as acetylation prevents the oxidation of aniline when the latter is nitrated with concentrated nitric acid, a strong oxidizing agent.

No elevation of the true sodium thiosulfate level was observed with a similar concentration of aminoacetic acid (glycine), NH_2CH_2COOH; urea, NH_2CONH_2; creatine, $NH_2C(NH)N(CH_2COOH)CH_3$; creatinine,



guanidine hydrochloride, $(NH_2)_2$ $CNH \cdot HCl$: or glutamic acid, $HOOC(CH_2)_2$-$CH(NH_2)COOH$.

A chemical method is available for the determination of sodium thiosulfate in which no iodine monochloride is formed. This is the "direct" method given by Newman et al. (3) for use with urine or the "iodide" method of Gilman et al. (2) for plasma filtrates and urine. These procedures vary only in the amount of potassium iodate used, since in each the material to be titrated is alkalinized before the addition of the appropriate amount of potassium iodate solution, so that no iodine monochloride can be produced. Then potassium iodide and hydrochloric acid are added in that order. The liberated iodine is immediately titrated with sodium thiosulfate. When the titration is performed immediately, a multifold excess of PAH causes no elevation of the true concentration of sodium thiosulfate. However, since this method is only an eighth as sensitive as the indirect method, it is not suitable for such low concentrations of sodium thiosulfate as 20 mg. per cent.

PAH is reported to cause false elevations of mannitol determination when these substances are used together in clearances. Early in 1947 Barker and Clark (5) observed an elevation of 0.25 to 0.30 mg. per cent in the true mannitol level for each mg. per cent PAH present in low, intermediate and high concentrations. The method for determining mannitol involves the oxidation of mannitol by a known excess of acid potassium periodate solution with the aid of heat. The potassium

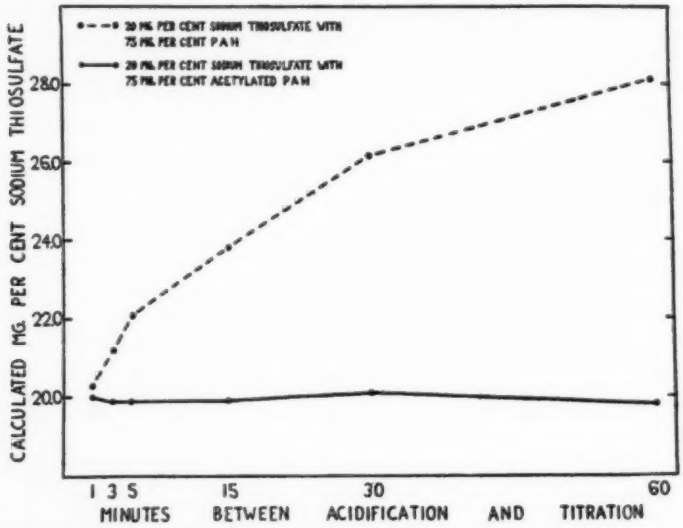


FIG. 2. COMPARISON BETWEEN THE EFFECTS OF PAH AND ACETYLATED PAH ON SODIUM THIOSULFATE DETERMINATIONS

iodate which is formed plus the residual potassium periodate is then determined by thiosulfate titration. Barker and Clark attributed the false elevation of mannitol values to the oxidation of PAH by periodate.

These authors developed a modified method for mannitol determinations in which PAH is acetylated and in this manner they are able to avoid false elevations of mannitol. Similarly acetylated PAH causes no false elevation of sodium thiosulfate values as illustrated in Figure 2. An attempt was made to introduce acetylation of PAH into the in-

direct procedure for thiosulfate determination. However, under the conditions employed in several experiments only irregular partial recovery was obtained with known sodium thiosulfate solutions containing high concentrations of PAH.

As suggested by Newman (4) cooling of the aliquot of serum filtrate in an ice bath for at least one hour prior to the addition of potassium iodate and hydrochloric acid permits the use of a five minute interval at room temperature when the PAH concentration is 75 mg. per cent. In the absence of PAH cooling does not appear to appreciably affect either the determination of the serum blank or the determination of sodium thiosulfate in serum filtrates. As would be expected, warming of the aliquot greatly increases the false elevation of the sodium thiosulfate level.

If the entire procedure, with the exception of the titration of the liberated iodine, is performed in the dark the same false elevation is observed as when light is present. In an effort to reduce the PAH concentration of the aliquot to a level at which it would not interfere, threefold dilution of the aliquot was made before the addition of potassium iodate and hydrochloric acid. After five minutes the iodine was liberated and immediately titrated. The false elevation is thereby diminished by approximately one mg. per cent. With sixfold dilution no further depression of the false elevation is observed. Twofold dilution does not diminish the false elevation at all.

CONCLUSIONS

1. In the presence of high concentrations of PAH false elevations of sodium thiosulfate levels occur when the "indirect" method of Newman et al. is used.

2. These false elevations increase with the time interval between acidification and titration in the "indirect" method of thiosulfate determination.

3. In order to obtain accurate values for sodium thiosulfate in the presence of PAH by this method the following factors must be observed:

(1) With low PAH concentrations the time interval should be,
   (a) Five minutes for serum filtrates
   (b) Three minutes for citrated and oxalated plasma filtrates

(2) With high PAH concentrations the time interval should be,
  (a) One minute for uncooled serum and plasma filtrates
  (b) Five minutes for thoroughly chilled serum filtrates.

4. Acetyl-PAH does not cause false elevations of sodium thiosulfate levels, and a satisfactory method for acetylation of PAH in this procedure is needed.

SUMMARY

The effect of para-aminohippuric acid on sodium thiosulfate determinations in renal clearance studies has been assessed. False elevations of thiosulfate are observed in the presence of PAH under certain conditions. Investigation of these elevations is detailed and suggestions are made for their avoidance.

We are indebted to Dr. Elliot V. Newman, Dr. J. Logan Irvin and Dr. Richard J. Bing whose helpful advice and criticism aided greatly in this project.

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THERAPEUTIC EVALUATION OF ISO-PAR* IN OTITIS EXTERNA

JAMES S. WALKER

From the Department of Surgery, Division of Otolaryngology, Johns Hopkins University and Hospital

Received for Publication March 24, 1948

The search for an antibacterial, antipruritic agent efficacious in the treatment of otitis externa has been a continuous one. The multiplicity of medications now in use is sufficient proof of this statement. The development of Iso-Par has provided us with a valuable addition for therapy of this obstinate condition. This article reports the results obtained with this ointment in acute and chronic otitis externa. No attempt was made at selection of patients nor was emphasis placed upon the bacteriological findings. Instead, the clinical picture and course were the determining factors in evaluation.

Reardon (1) found that the use of Iso-Par was far superior to any other type of treatment he had used previously in his experience with otitis externa in the army. During a period of two years in the tropics, he was able to observe several hundred patients with disease. He concluded that the ointment was definitely beneficial, non-toxic, locally anesthetic, and bactericidal in its action.

Iso-Par is a suspension of paraffinic acids in a base of lanolin and petrolatum. Although in vitro tests are inconclusive, definite bactericidal and fungicidal properties may be assigned to this ointment.

The routine office treatment was simple and expedient. With alcohol soaked applicators the ear canal was carefully cleansed of all debris and discharge. A thin coating of ointment was then applied. This procedure was repeated in the clinic during the acute phase of the infection as often as necessary. Later the patient was instructed in the application of the ointment at home. Supportive symptomatic

* Iso-Par is a mixture of water insoluble isoparaffinic acids partially neutralized with *iso*cytyl hydroxybenzyl-dialiphatic amines. Iso-Par unguentum contains 17 per cent of Iso-Par and 4 per cent of titanium dioxide in an ointment base consisting of beeswax, cetyl alcohol, lanolin, and petroleum. U. N. R., 1947. p. 90.

care in the form of heat, aspirin, and codeine was prescribed as indicated.

Subjectively, the annoyance of itching and the relief of pain were noticed usually after the initial application of the ointment. With the abatement of these symptoms it was much easier to care for the affected ear on the succeeding visits. In those patients suffering from recurrent infections, the prophylactic use of Iso-Par once a week was advised.

Forty-one patients are considered in the present report. Many others were treated but did not return to the clinic. Twenty-three acute and eighteen chronic cases of otitis externa are summarized. A case was classed as chronic if symptoms had persisted over three months or history indicated the infection was a recurrent one. For study, a division was made according to the severity of the infection. Thus, the mild cases were those patients who exhibited some itching and occasional discharge from the ear. The patients who had findings of moderate discharge, redness, edema, and complained of pain were considered moderately severe infections. All those with the above findings present, plus evidence of a cellulitis of the soft tissues of the ear canal and surrounding area, were classed as severe.

In the accompanying table, it will be seen that the patients' ages varied from eleven to seventy years. Except for two circumscribed infections, the usual picture was that of diffuse involvement. Twenty-nine, or almost two-thirds of the cases, were of the "moist" variety, in contrast to the dry or non-eczematous type seen in the remainder. The former are usually most resistant to therapy.

Following the regime as outlined, it was possible to class twenty-five or sixty per cent as cured; ten or twenty-four per cent as improved; and six or only sixteen per cent as unimproved. No average length of treatment period could be established. Some patients required constant care over a two month period before finally clearing, while others required therapy for only five to seven days.

The results of the series reported here are in agreement with the impressions gained by Reardon. Iso-Par has proven to be of definite value in the treatment of otitis externa. No sensitization to the drug was seen. It relieved pain and pruritis by its local action.

Summary of Results with Iso-Par in Otitis Externa

PATIENT	AGE	RACE SEX	ACUTE	CHRONIC	MOIST	DRY	UNILATERAL	BILATERAL	PREVIOUS R	DAYS ISO-PAR	CURED	IMPROVED	UNIMPROVED	DEGREE
1 AH	47	cf	No	Yes	Yes	No	No	Yes	No	14	Yes	No	No	Sev.
2 HC	43	wm	Yes	No	Yes	No	No	Yes	Yes	45	No	No	Yes	Sev.
3 AC	60	wf	No	Yes	Yes	No	No	Yes	No	12	No	Yes	No	Sev.
4 CM	53	wm	Yes	No	No	Yes	No	Yes	No	14	Yes	No	No	Mild
5 WO'M	31	wm	Yes	No	Yes	No	Yes	No	No	12	No	Yes	No	Sev.
6 AP	36	cm	Yes	No	Yes	No	Yes	No	No	10	Yes	No	No	Mild
7 MA	25	wf	Yes	No	Yes	No	Yes	No	No	7	Yes	No	No	Mod.
8 BH	20	wf	No	Yes	Yes	No	No	Yes	No	21	Yes	No	No	Sev.
9 EM	47	wm	Yes	No	Yes	No	Yes	No	No	3	No	No	Yes	Sev.
10 EC	45	wf	Yes	No	Yes	No	No	Yes	No	8	No	No	Yes	Sev.
11 AR	27	wf	Yes	No	No	Yes	No	Yes	No	60	Yes	No	No	Sev.
12 JK	23	wm	No	Yes	Yes	No	No	Yes	Yes	30	No	Yes	No	Sev.
13 LA	25	cm	Yes	No	Yes	No	Yes	No	Yes	4	No	No	Yes	Mod.
14 JM	19	wm	Yes	No	Yes	No	Yes	No	No	24	Yes	No	No	Sev.
15 DT	8	wm	Yes	No	Yes	No	Yes	No	No	6	Yes	No	No	Sev.
16 DF	44	cf	Yes	No	Yes	No	Yes	No	No	13	Yes	No	No	Sev.
17 EJ	38	wf	No	Yes	No	Yes	No	Yes	No	5	No	No	Yes	Mod.
18 EE	32	wf	Yes	No	Yes	No	Yes	No	Yes	60	No	Yes	No	Sev.
19 SF	68	wf	No	Yes	No	Yes	No	Yes	No	21	Yes	No	No	Mod.
20 AS*	26	wf	No	Yes	Yes	No	No	Yes	No	14	Yes	No	No	Mod.
21 AC	24	cf	Yes	No	Yes	No	No	Yes	No	3	Yes	No	No	Mod.
22 PW	33	wf	No	Yes	Yes	No	No	Yes	No	7	No	Yes	No	Mod.
23 LJ	63	wf	No	Yes	No	Yes	No	Yes	No	5	Yes	Bo	No	Mod.
24 WJ	20	wm	No	Yes	No	Yes	No	Yes	Yes	4	Yes	No	No	Mild
25 LB	36	wf	No	Yes	Yes	No	No	Yes	Yes	7	No	Yes	No	Sev.
26 MT	70	wm	Yes	No	Yes	No	No	Yes	No	6	Yes	No	No	Mod.
27 AM	22	wm	Yes	No	Yes	No	Yes	No	No	7	Yes	No	No	Mod.
28 AW	11	wf	Yes	No	Yes	No	Yes	No	No	21	No	No	Yes	Mod.
29 SV	11	wf	No	Yes	Yes	Nc	Yes	No	Yes	9	Yes	No	No	Mild
30 PC	59	wm	No	Yes	Yes	No	No	Yes	Yes	67	Yes	No	No	Mod.
31 MH	68	wf	Yes	No	No	Yes	No	Yes	No	5	Yes	No	No	Mild
32 TM	15	cf	No	Yes	Yes	No	No	Yes	Yes	13	Yes	No	No	Mod.
33 EB	44	cf	Yes	No	No	Yes	No	Yes	No	7	Yes	No	No	Mild
34 MJ	53	wf	No	Yes	No	Yes	No	Yes	No	35	No	Yes	No	Mod.
35 PH	56	wf	No	Yes	No	Yes	Yes	No	No	4	Yes	No	No	Mild
36 GR	14	cf	Yes	No	Yes	No	Yes	No	No	9	Yes	No	No	Sev.
37 MH	14	wf	Yes	No	Yes	No	No	Yes	Yes	7	Yes	No	No	Mod.
38 EB*	57	wm	Yes	No	No	Yes	Yes	No	Yes	7	Yes	No	No	Sev.
39 LT	33	cf	No	Yes	Yes	No	No	Yes	No	2	No	Yes	No	Mod.
40 SL	12	wf	Yes	No	Yes	No	Yes	No	Yes	9	No	Yes	No	Sev.
41 CD	46	cm	No	Yes	No	Yes	No	Yes	No	60	No	Yes	No	Mild
			23	18	29	12	16	25	12		25	10		8 Mild 16 Mod. 17 Sev. — 41

* Circumscribed lesions.

A high percentage of cures was effected within a minimum of time. It should be considered a valuable aid in therapy of otitis externa.

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PREFRONTAL LOBOTOMY FOR THE RELIEF OF INTRACTABLE PAIN

FRANK J. OTENASEK

Department of Surgery, Division of Neurosurgery, The Johns Hopkins Hospital

Received for Publication March 25, 1948

Pain, as a subjective experience, is a complex phenomenon. Psychologists still express some disagreement about whether pain is a sensation or an emotion. Looked upon as a sensation it has, in common with other sensations, a threshold, the possibility of localization, as well as reference to a stimulus. Unlike the other sensations, such as vision and touch, however, pain is involved much more closely with the center of personality and has a good deal in common with some of the emotions such as fear and guilt. Studies on pain in the physiological laboratory have almost entirely, but necessarily, been confined to the so-called "objective" data referable to thresholds, transmission of impulses, fatigability, and so on. It has thus far not been possible for physiological methods to differentiate between the purely sensory component of pain and the "unpleasantness" or the "reaction to pain" of the emotional element. This was placed in the realm of the psychologist (1).

Relief of pain is one of the primary concerns of the physician. All analgesic drugs, of course, have their place in the treatment of the occasional mild pain or pain of short duration, but where one is dealing with chronic or persistent pain the simpler analgesics are ineffective, while the narcotics carry the grave danger of addiction. Under these circumstances, the surgeon is frequently called upon to break the pathway of pain on the physiological level. This involves nerve-block, root section, chordotomy, or even resection of the sensory cerebral cortex. This surgical treatment, however, does not always produce the desired relief, either because of previous addiction to drugs, or because of the essentially subjective nature of the symptoms. It is important to bear in mind the difference between mere perception of pain and reaction to pain. The latter includes not only certain autonomic reactions such as sweating or tachycardia, but also the

emotional and attitudinal reactions, such as anxiety, fear, panic, or even prostration. It is failure to control the latter that makes so many surgical measures for relief of pain ineffective.

Considerable progress has been made in the treatment of intractable pain by prefrontal lobotomy. Freeman and Watts (2) noted that in their series of patients with nervous and mental disease upon whom prefrontal lobotomies were done, there were a number who had complained of unbearable pain. It is important that the complaints of these patients seemed to be out of all proportion to the painfulness of the condition giving rise to the complaints. After operation not only were the complaints no longer heard, but nervous tension, anxiety and apprehension disappeared. This experience led to the use of prefrontal lobotomy in patients who had intractable pain, but no nervous or mental disease which in itself justified lobotomy. Poppen (3), Sargent (4), and others have reported striking relief of painful conditions which had resisted other forms of surgical therapy, such as carcinoma, tabes dorsalis, and phantom limb pain.

Our own experience thus far has been limited to patients with incurable cancer, all individuals whose life expectancy was relatively short. In these patients it was clear that there was great pain, but nervous tension, apprehension and fear of pain all seemed to be factors of greatest importance.

Case Reports: It is interesting to consider the details in a few of our patients. I have picked out five which should be of interest.

Case 1. A.A., WM, 62. Three years before admission this patient developed hematuria. A bladder tumor was removed suprapubically in 1943. Five or six months before admission to the Brady Institute in October, 1946, he again developed hematuria and more tumor was removed cystoscopically. From then on he lost appetite, lost 20 pounds in weight and developed a rather severe low back pain which grew steadily worse. When seen here a large bladder tumor was demonstrated on the right side. This was thought to represent an infiltrating carcinoma, grade C, inoperable. Deep X-ray therapy was instituted, but the patient continued to have severe pain in the back. The patient was given 12 mgm. of morphine at first every four hours, later increased to every hour. About one month after his admission to the hospital he developed severe pain and swelling of the left leg and became bed-ridden. Inasmuch as this pain was unilateral and severe enough to cause increase of morphine administration to hourly intervals, a chordotomy was done. A satisfactory level of analgesia was obtained, but the patient began to complain more than ever of pain in his back and now his right leg. It was

necessary to continue hourly hypodermics as before. The patient was apprehensive, in a constant state of anxiety, anticipating both his pain and his hypodermics. Accordingly on January 8, 1947, three weeks after chordotomy, a prefrontal lobotomy was done. The patient became disoriented and confused and was incontinent both of urine and feces. These symptoms gradually improved. Six weeks after operation there were still a few aberrations, such as an apparent desire to get into other patients' beds, or to get into the tub for a bath and turn on the hot water without regard for burning himself. From the moment of operation it was clear that he either had no pain, or that it did not bother him. When asked whether he had pain he either denied it, or replied "Yes, but it doesn't bother me." Although he had received morphine or Schlesinger's solution every hour for nearly two months before lobotomy, he did not now require even an aspirin tablet. He was apathetic not only about the pain, but looked upon the hopelessness of his fate, and even impending death, with complete equanimity. This in spite of a previous state of anxiety and great apprehension. Only one glance at him sufficed to show that he was comfortable. He was no longer bed-ridden, but could walk about quite normally. His course after leaving the hospital on March 1, 1947, is unknown.

Case 2. T.B., CM, 58. This patient was admitted to the Osler Medical Service on August 29, 1946, complaining of pain in the chest and back of two months' duration. Four days before his admission he developed weakness and numbness of his legs. Within twenty-four hours there was complete paralysis of the legs and anesthesia up to the umbilicus. He developed a cord bladder and fecal incontinence. On examination a carcinoma of the prostate could be palpated. Subsequent biopsy revealed a poorly differentiated carcinoma. Spinal puncture revealed a complete block. Because of the rapid course of the paralysis with fever and severe localized pain and tenderness at T6, a laminectomy was done with the hope of finding an epidural abscess, but none was disclosed. Widespread bony metastases were later discovered. The patient continued to have severe pain in his chest and he was placed on amidone in doses about equivalent to morphine. This gradually became ineffective and by early November he was taking as much as 32 mgm. of morphine every two hours. Tubo-curare was also tried but was not significantly effective. The patient was quite apprehensive and asked for his medicine by the clock. On February 5, 1947, prefrontal lobotomy was carried out. He became confused and disoriented, but gradually regained recognition of his family. It is interesting to read the medical house-officer's comments of two weeks after operation: "Clinically Thomas is, of course, no better, and the appearance of his bed sores is appalling (he had, of course, had these before operation). Mentally, however, he is indeed a new man. He realizes that he is sick and that he is in pain from time to time, but it does not bother him one whit. He tells us that he feels just fine and I'm sure he means it." Because of apparent restlessness, two doses of sodium luminal were given in the seven weeks' interval between his operation and his death of generalized carcinomatosis.

Case 3. D.L., WF 52. Two years before this patient's admission to the hos-

pital she began to have attacks of sore throat and difficulty in swallowing. In the fall of 1945 she went to another clinic where a biopsy of a tumor in the neck was taken and she was told she had a carcinoma of the larynx. X-ray therapy was given. In April, 1946, she was given further X-ray therapy and a tracheotomy was done. Three months prior to her first admission here she developed pains in the chest and paroxysmal painful coughing which was non-productive. The pain was constantly increased by deep respiration. There had been no loss in weight. Admission to the Surgical Service took place on November 24, 1946. She had a tracheotomy tube in place. No growth could be seen or felt in the neck. No tumor of larynx or branchus could be found by bronchoscopy. X-ray showed a mass in the right lower lobe of the lung. On December 13, 1946, exploratory thoracotomy was performed and an inoperable tumor of the lung was found. The tumor mass had eroded through the diaphragm to involve the liver. There were large mediastinal nodes. The patient was discharged on December 30, 1946, with the diagnosis of inoperable carcinoma of the lung. Following discharge the patient gained a little weight, but had a frequent painful cough and almost constant complaint of pain in the lower chest. This spread up over the chest wall and began to involve the right arm. She was taking narcotics about every four hours, was quite tense and feared her cough. Pain gradually grew worse and she was readmitted on February 26, 1947. A week later prefrontal lobotomy was carried out. Following this she had no complaint of pain and no sedatives were required. On questioning at times she admitted having pain, but was obviously not uncomfortable. Interestingly enough, once her apprehension was removed, her cough nearly ceased altogether. The tracheotomy wound was closed. This patient showed no confusion or disorientation. She was the intelligent wife of an intelligent man. Before discharge from the hospital on March 19, 1947, he was asked if he noted any change in her personality. At first he said there was none, then modified the statement to say that perhaps there was but it was so subtle he could not tell what it was. The patient was usually continent at the time of discharge two weeks after operation, but still occasionally voided in bed.

Case 4. S.S., WF, 61. This patient was admitted March 20, 1947, because of intractable pain in the face and head. About three and one-half years before she had developed a painless swelling at the angle of the left mandible. A sarcoma was removed and deep X-ray therapy, as well as Radon implantation was carried out. For three years she had constant, severe pain involving the entire left side of the head. There was continuous complaint. The patient was worried. Codeine and empirin were taken in large doses. Lobotomy was performed on March 22, 1947. Her complaints of pain stopped instantly and no more medication was required. On the fourth day after operation the patient began to run an unexplained fever, the cause of which was difficult to track down because there was no complaint of pain. About two days later it was discovered that the patient had a diffusely tender and rigid abdomen. X-rays revealed the presence of free air beneath the diaphragm and the diagnosis of perforated peptic ulcer with peritonitis was made. Because of the hopeless nature of the patient's tumor, no surgical

therapy was instituted and she died on the tenth day after lobotomy. Autopsy confirmed a perforation of a chronic peptic ulcer and showed a fibrinopurulent peritonitis. In addition there was a fresh coronary thrombosis.

In view of the known excruciating character of the pain from an acute perforation of a peptic ulcer, it is interesting that this patient made no complaint and seemed not uncomfortable. Yet she reacted in perfectly normal fashion to palpation of or pressure on the abdomen, wincing when this was done and showing the characteristic rigidity of the abdominal wall.

Case 5. M.W., CF, 26. This patient was first admitted to the hospital in 1936, when she had several radical sinus operations, with uneventful recovery. In January, 1947 she was readmitted with a history of frontal headaches for about one month. X-rays showed what appeared to be a huge osteoma involving the left frontal bone, the orbit, and the floor of the anterior fossa of the skull. In February, 1947, operative removal of the osteoma was attempted, but was not successful because of the size, the infiltration and vascularity of the tumor. Pathologically it proved to be a carinoma, probably arising in the nasal sinuses. The patient continued to have severe pain in the face and the left frontal region. On September 5, 1947, a prefrontal lobotomy was done. The patient at this time was about seven months pregnant. At the time of discharge, on the fifth postoperative day, she was confused, disoriented and incontinent, but had no pain. When seen a week later she seemed very happy and the family felt she was getting along very well without medication. On September 20, 1947, this patient was delivered of a normal, premature infant without anesthesia or analgesia, following a labor of five hours. Her reactions to the labor pain were interesting in that they appeared to be those of a normal woman under the influence of sedation. In other words, when a pain came, she screamed and yelled in ordinary fashion, but as soon as the pain was over she relaxed in perfectly normal manner and had no fear or anticipation about the next pain.

In addition to these five cases which have been described in some detail, there have been six others, with carcinoma of the kidney, the neck, breast, cervix and colon, and one case with a combined long standing carcinoma of the nose with a more recent carcinoma of the prostate. One patient died of intracranial hemorrhage three days after operation; the others are either free of pain and receiving no medication, or have died of their cancer.

COMMENT

Examination of all these patients after operation makes it clear that prefrontal lobotomy alters the individual's reactions to pain without materially changing his ability to feel pain. Ordinary tests of pain perception by pin-prick or other methods reveal that the

patient's perception of pain is unchanged. When stuck with a pin such a patient will wince, but it may be difficult to make him angry by repeatedly sticking him. The patient who died of peritonitis following perforation of a peptic ulcer showed a normal amount of tenderness and rigidity in the abdomen, yet never once complained of abdominal pain.

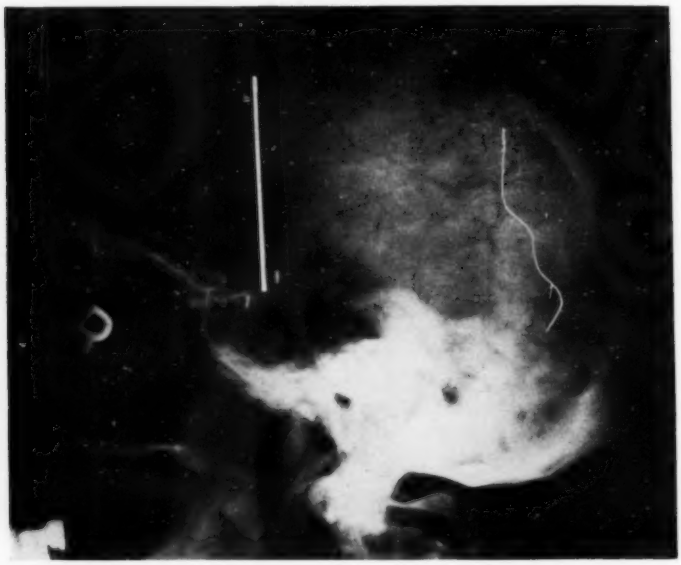

FIG. 1. Showing so-called ideal plane of section from coronal suture to sphenoidal ridge.

From the study of our cases it becomes clear that the real indications for lobotomy in cases of intractable pain are based in large part upon the emotional component; i.e., the "reaction" of the individual to his pain with anxiety, discouragement and apprehension. Prefrontal lobotomy will eliminate this affective component in a striking manner. In brief, it seems that when the fear of pain is abolished, the perception of pain itself is not intolerable. In the words of Freeman and Watts, "Pain may be present, but when divorced from its implication—

insecurity, disability, guilt, death—it then becomes bearable and may be accepted with fortitude.'' The fear of impending death and the hopelessness of the situation are removed to the extent that the patient's prognosis can be discussed with him quite openly and truthfully. He is no longer afraid to die.

Prefrontal lobotomy relieves pain by interrupting the pathways at a psychologic rather than a physiologic level. There is no specificity

FIG. 2. The section in this case was considerably anterior to the ideal; yet the patient was relieved of pain.

for pain; relief depends upon alteration of affective aspects of the personality. For this reason partial lobotomies or attempted differential lobotomies have thus far been unsuccessful. All four quadrants of both frontal lobes must be severed. There is much to learn, however, about proper level of section.* Theoretically, a proper lobotomy involves severance of the white matter from the coronal suture to the sphenoidal ridge. Whether this extensive procedure is always neces-

sary in patients with intractable pain remains to be seen. It appears that the larger the section, the greater the alteration of personality.

The use of prefrontal lobotomy in patients with intractable pain has opened up a large field for study by psychiatric and psychologic methods. Research on the influence of the frontal lobes on personality and intelligence now may be attacked in much more direct fashion. This was not very often possible in the cases of lobotomy in psychotics, because proper pre-operative standards frequently could not be established. The cases presented in this series were not suitable for such a study because in every case post-operative life expectancy was so short that, although the patient was relieved of pain, his psychic functions did not often have time to reach their ultimate base line. Lobotomies done on patients with phantom limb pain, tabes dorsalis, or other non-lethal painful states will supply much more opportunity for study.

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* Figures 1 and 2 indicate the possibility of variation in the level of section. In Figure 1 the so-called "ideal" plane of section is accomplished, the cut being made from the coronal suture to the sphenoidal ridge. In Figure 2 the section is a considerable distance anterior to this. In both instances the lobotomy brought relief of pain. In the first there was a major degree of personality alteration in addition. In the second, although pain relief was complete, there was no detectable gross alteration of personality. This comparison may indicate the direction of future work.

THE CARDIAC MECHANISM DURING ANESTHESIA AND OPERATION IN PATIENTS WITH CONGENITAL HEART DISEASE AND CYANOSIS

ROBERT F. ZIEGLER

Received for publication April 2, 1948

From the Departments of Pediatrics and Surgery, The Johns Hopkins University and Hospital, Baltimore, Maryland

The purpose of the present study is twofold: (1) to determine the mechanism, significance, and management of the cardiac arrhythmias occurring during anesthesia and operation in children with congenital heart disease and cyanosis; and (2) to determine the preterminal cardiac mechanism in the children who die during this period. The importance of the latter problem, and what if anything might be done about it, is established by the relatively high incidence of death during operation, exceeded only by cerebral thrombosis as a single cause of death in the operative series.

The need for more adequate information concerning the cardiac mechanism during anesthesia and operation is apparent upon reviewing the available literature. Widely varying opinions have been expressed, with the result that a serious degree of confusion still exists about methods for the prevention and management of important cardiac arrhythmias. Certain shortcomings, more or less common to the majority of the studies published, are probably responsible for these variations of opinion, and include the following: (1) limited numbers of cases; (2) insufficient control of numerous and important variable factors; (3) dependence on the results of animal experiments without any necessarily direct comparison with results in human subjects; and (4) frequent lack of direct electrocardiographic evidence to support proposed hypotheses. Although it is not claimed that all of these criticisms have been avoided in the present investigation, the unusual opportunity for studying the heart's action during anesthesia and operation, especially under conditions of anoxia, has been productive of results which have appeared to be worthy of publication.

MATERIALS AND METHODS

Patients selected for the study included 175 consecutive children with congenital heart disease and cyanosis submitted to the Blalock-

Taussig operation (8) for the correction of the abnormal circulatory dynamics of pulmonic stenosis with intracardiac right-to-left shunt. Three standard extremity leads were recorded almost continuously using a direct-writing electrocardiograph. Preoperative medication consisted of morphine (1 mg. per 5 kg. body weight) and atropine (0.05 mg. per 5 kg. body weight) given hypodermically. Induction was accomplished with cyclopropane and oxygen; and this mixture with the addition of ether in small amounts, given intratracheally, was continued throughout operation except for changing in certain individuals to just ether and oxygen or occasionally to oxygen alone (12). Similar electrocardiographic records were made in a control group including: ligation of a patent ductus arteriosus, 15 cases; surgical correction of coarctation of the aorta, 3 cases; and resection of the pericardium for constrictive pericarditis, 2 cases.

RESULTS

The general incidence of disturbances of the cardiac mechanism during anesthesia and operation in this series of children with congenital heart disease and cyanosis is approximately the same as in the non-cyanotic group and in other reported series of various types of operations in which cyclopropane was the chief anesthetic agent (16). This observation would appear to confirm the statement that the anesthetic agent is of greater importance than the type of operative procedure in the production of cardiac irregularities. The types of disturbance in the cardiac mechanism are also generally similar to those reported in other studies (10, 16, 20, 30, 31, 32), and may be classified as follows:

1. Simple variations in rate
   - Sinus tachycardia
   - Sinus bradycardia
2. Ectopic arrhythmias
   - A. Displacement of the normal pacemaker
     - Atrio-ventricular nodal rhythm
   - B. Premature contractions and paroxysmal tachycardia
     - Auricular
     - Nodal
     - Ventricular

3. Abnormalities of the form of the ventricular deflections
   - Minor aberration of QRS
   - Bundle branch block
   - ST segment deviation
   - T wave inversion
4. Disturbances of conduction
   - PR interval
   - QT interval
5. Terminal mechanisms
   - Cardiac arrest
   - Complete A-V dissociation
   - Idioventricular rhythm
   - Ventricular fibrillation

For further details reference may be made to Tables I and II.

Variations in heart rate with normal sinus mechanism are seldom of any significance. Sinus tachycardia was found to occur during all stages of operation and could be attributed in many instances to the effect of atropine given either as a routine preoperative medication or during the course of anesthesia and operation. Sinus bracycardia, on the contrary, was most frequently observed under circumstances apparently favoring vagal stimulation as evidenced by the fact that it was abolished in most cases by the administration of atropine (Fig. 1).

Ectopic arrhythmias are of two general types depending on their mode of origin. They may result from (1) depression of the rhythmicity of the normal cardiac pacemaker (sino-auricular node) with supercedence of a center of otherwise lesser degree of rhythmicity, or (2) increased irritability of any portion of the heart, the new focus gaining control over the normal cardiac mechanism by virtue of its abnormal rhythmicity or by circus movement of the extopic impulse. Arrhythmias of the first sort were most common, occurring in more than half of the children. In all instances this took the form of some type of nodal rhythm which maintained temporary control of both ventricles and auricles, the latter by retrograde conduction, or of the ventricles alone, the auricles responding to a slow sinus rhythm. Various types of nodal rhythm observed included the following: (1) nodal rhythm with absence of visible P waves which are presumably superimposed in QRS (Fig. 1A and 2A), 24.7%; (2) classical AV nodal

TABLE I

	CYANOTIC	TERMINAL	NON-CYANOTIC	TERMINAL
Number of cases	165	10	19	1
Incomplete	7		0	
Total	158	10	19	1
Regular throughout	35 (22.1%)	0	5 (26.3%)	0
Displacement of the normal pacemaker	88 (55.7%)	6 (60%)	6 (31.5%)	1
Abnormal rate	44 (27.8%)	10 (100%)	7 (37%)	
Sinus tachycardia	27 (17.1%)	9 (90%)	6 (31.5%)	1
Sinus bradycardia	17 (10.7%(	10 (100%)	2 (10.5%)	0
Premature contractions	14 (8.9%)	5 (50%)	4 (21%)	0
Auricular	1 (0.63%)	0	0	
Ventricular	12 (7.6%)	3 (30%)	4 (21%)	
AV nodal	1 (0.63%)	2 (20%)	0	
Aberration of QRS	14 (8.9%)	4 (40%)	3 (15.8%)	0
Bundle branch block	0	2 (20%)	0	1
Paroxysmal tachycardia	7 (4.4%)	7 (70%)	1 (0.05%)	
Auricular	7 (4.4%)	2 (20%)	0	
Ventricular	0	3 (30%)	0	1
ST segment deviation	7 (4.4%)	3 (30%)	0	0
T wave inversion	2 (1.26%)	0	0	0
Prolongation of PR interval	1 (0.63%)	0	0	0
Prolongation of QT interval	1 (0.63%)	0	0	0
Sinus arrest	1 (0.63%)	9 (90%)	0	1
AV dissociation	0	9 (90%)	0	0
Terminal asystole	0	7 (70%)	0	1
Ventricular fibrillation	0	1 (10%)	0	0

rhythm with inverted P waves either preceding QRS with a short PR interval or immediately following QRS (Fig. 2B and C, 6C, 7B), 19.0%; (3) AV nodal rhythm with interference dissociation (Fig. 7C and D), 12%; (4) coronary nodal rhythm with upright P waves and

short PR interval (Fig. 1G and 2D), 7.6%; and (5) high nodal rhythm with inverted P waves preceding QRS with a normal or only slightly shortened PR interval (Fig. 6C), 5.7%. Although these various types of disturbance appear superficially to represent a single basic mechanism, it seems likely from a more detailed analysis that they

TABLE II

	TOTAL NO.	ANESTHESIA	MEDIASTINAL EXPLORATION	ANASTOMOSIS	CLOSING
Displacement of normal pacemaker	88	36	48	49	29
Tachycardia	27	3 (4)	2 (4)	8 (4)	1 (4)
Bradycardia	17	8	9	0	0
Premature Contraction					
Auricular	1	0	0	1	0
Ventricular	12	4	6	2	0
Nodal	1	0	1	0	0
Aberration of QRS	14	2 (7)	3 (7)	2 (7)	0 (7)
Paroxysmal tachycardia					
Auricular	7	1	1	0	5
Ventricular	0	0	0	0	0
ST segment deviation	7	0	0	7	0
T wave inversion	2	2	(2)	(2)	(2)
Prolongation of PR interval	1	0	0	1	0
Prolongation of QT interval	1	0	0	1	0

result from the interaction of at least two different mechanisms. Thus, it was observed that the ventricular rate during AV nodal rhythm exceeded that during the preceding normal sinus rhythm in 33 instances (25.5%), remained the same in 67 (51.9%), and was slower in 29 (22.6%). The latter group is probably the only one that represents a true passive nodal rhythm, with depression of the normal pace-

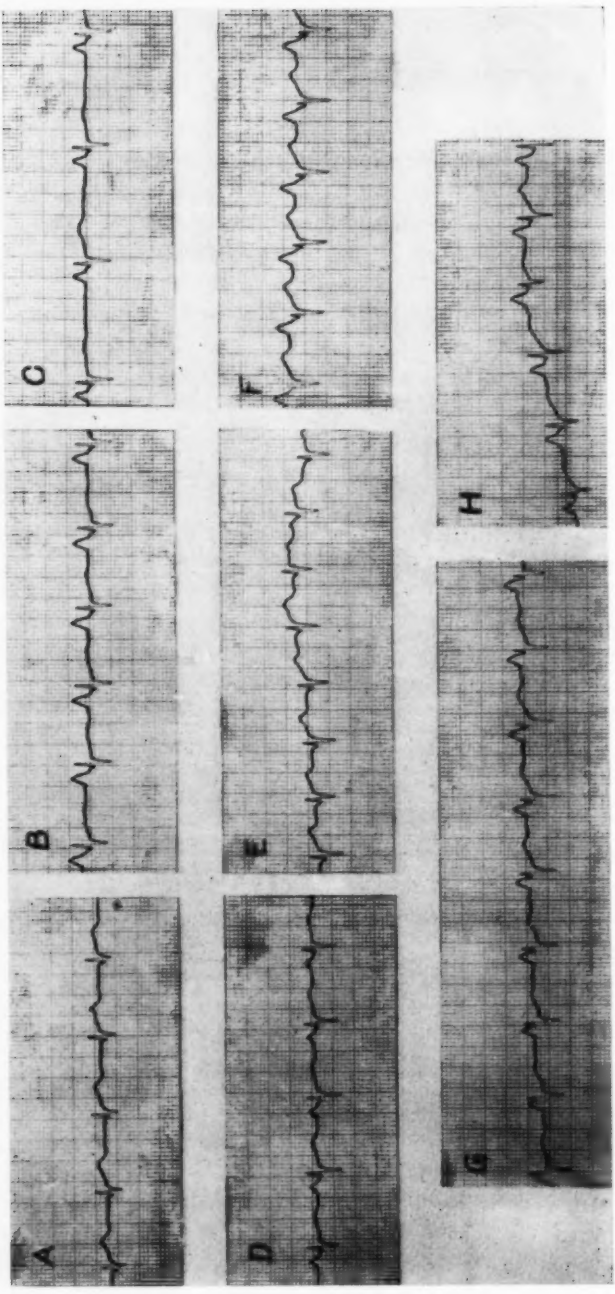


FIG. 1

maker (SA node) and supercedence of a center of lower rhythmicity (AV node). The first group, with a faster ventricular rate by virtue of an abnormally increased degree of rhythmicity of the AV node (Fig. 1E), appears to belong to what may more properly be termed an active ectopic nodal tachycardia. The intermediate group probably comprises both mechanisms, that is, abnormal depression of the rhythmicity of the SA node together with abnormal acceleration of that of the AV node. In support of the foregoing concept are data derived from an analysis of the response of the heart controlled by the AV node to the administration of atropine. More than half of the cases (46, 52.3%) reverted spontaneously to normal sinus rhythm; 19 (21.6%) reverted with atropine (Fig. 2A and C); 8 (9.1%) were basically unaffected by atropine; and 15 (17%) could not be classified. In all instances of slow nodal rhythm, reversion to a normal sinus mechanism was accomplished by the administration of atropine, indicating that the stimulus for depressing the normal rhythmicity of the sino-auricular node was probably mediated by way of the vagus nerves. Those that failed to respond to atropine, on the contrary, were all instances of fast nodal rhythm or nodal tachycardia, indicating that the primary mechanism in this group was something other than vagal depression of the normal cardiac pacemaker. That vagal stimulation might be exerting at least a minor influence in this group, however, was evidenced by the fact that in several instances the ventricular rate, though still controlled by the AV node, became more rapid after the administra-

FIG. 1. R. K., AGE 22 YEARS, TETRALOGY OF FALLOT.
AV NODAL RHYTHM. LEAD 2

A. Nodal rhythm with absent P waves, rate 80; during anesthesia.

B. Spontaneous normal sinus rhythm, rate 84 (without atropine).

C. Sinus bradycardia, rate 55; mediastinal exploration.

D. Normal sinus rhythm after atropine, rate 84, difference in the form of the P waves from that of earlier and later portions of the record; mediastinal exploration.

E. Fast nodal rhythm with P superimposed in QRS, rate 106; during anastomosis.

F. Normal sinus rhythm, rate 88.

G. Nodal rhythm with dissociation, variation in the relation of P to QRS; during anastomosis.

H. Normal sinus rhythm, rate 94; closing chest.

FIG. 2

tion of atropine (Fig. 1E, 2C). Nodal rhythm of the various types listed occurred with nearly equal frequency during anesthesia and throughout all phases of operation and was not related to any specific operative procedure. It may therefore be assumed that, while direct vagal stimulation as in mediastinal exploration and manipulation of the great vessels may be responsible for the occurrence of such arrhythmias, they may also result from action of the anesthetic agent mediated by way of the vagus nerves as well as by direct action on the myocardium and the specialized tissues of the heart. The effect of preoperative medication also must be considered, morphine tending to exaggerate the arrhythmias in part perhaps by vagal stimulation, and atropine failing to protect the heart against such irregularities in the amounts usually given (11). It may be stated that morphine is claimed to have a protective effect against ectopic arrhythmias such as cyclopropane-epinephrine tachycardia (3).

Arrhythmias due to increased cardiac irritability, including premature systoles and paroxysmal tachycardia, occurred in a total of 21

FIG. 2

FIG. 2. FOUR CASES DEMONSTRATING VARIOUS TYPES OF NODAL RHYTHM

A. T. S., age 6 years, tetralogy of Fallot. Lead 3.

Normal sinus rhythm, rate 110, spontaneous variation in form of QRS.

Nodal bradycardia with absent P waves, rate 75; mediastinal exploration.

Normal sinus rhythm after atropine.

B. A. M., age 5½ years, tetralogy of Fallot. Leads 1, 2, and 3.

Normal sinus rhythm, rate 120.

Nodal rhythm with inverted P wave preceding QRS by slightly shortened PR interval; opening of anastomosis.

C. R. K., age 15 years, tetralogy of Fallot. Lead 2.

Inverted P wave following QRS, rate 65; pre operative.

AV nodal rhythm with apparently "premature" systoles arising from normal pacemaker in SA node.

Nodal tachycardia after atropine, rate 115. P waves at first inverted and following QRS, later absent.

Normal sinus rhythm, rate 106.

D. M. C., age 2 years, tetralogy of Fallot. Lead 3.

Normal sinus rhythm, rate 150.

Nodal rhythm with upright P wave preceding QRS with short PR interval, rate 96; during anastomosis.

Nodal rhythm, emergence of P wave from QRS.

Normal sinus rhythm occurring spontaneously, rate 150.

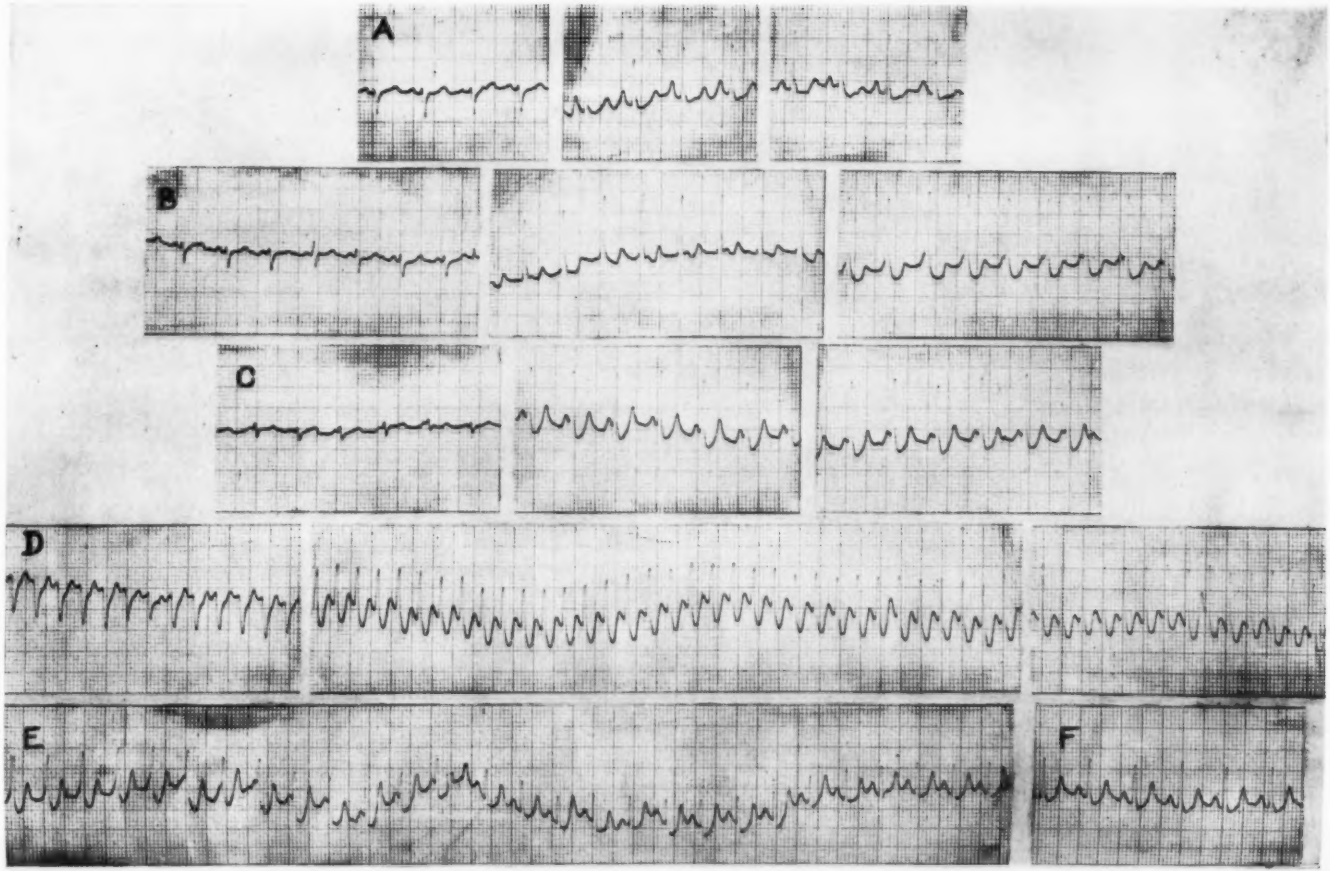


FIG. 3

patients (13.3%). Of the premature contractions, 12 of the 14 were ventricular; most occurred early in operation; and at least half were definitely due to cyclopropane, disappearing rather promptly after changing the anesthetic mixture to ether and oxygen (Fig. 4). Auricular premature systoles occurring in one case were due to direct stimulation of the right auricle; and nodal premature systoles in one were apparently the direct result of manipulation of the vagus nerve. Paroxysmal tachycardia, except when arising in the AV junctional tissues, was of auricular origin in every case of the surviving group. The majority of instances (5 of 7, 71.5%) occurred at the end of operation during chest closure (Fig. 3), one during anesthesia before the chest was opened, and one during mediastinal exploration and anastomosis. The cause of this disturbance of the cardiac mechanism is not clear, although it is known, and was observed in this series, that stimulation of the vagus nerve tends to abolish the arrhythmia whereas paralysis of the vagus by atropine tends to perpetuate it.

Another type of disturbance of the cardiac mechanism, which can be detected only by electrocardiography, is the group of abnormalities of the form of the ventricular deflections. In this group are included minor aberration of the form of QRS 14 (8.9%), ST segment deviation 7 (4.4%), and T wave inversion 2 (1.3%). Minor variations in the form of QRS, of academic interest but apparently of no great clinical significance, ranged from slight changes in the amplitude of the ventricular deflections (Fig. 3B) to gross reversal of the direction of

FIG. 3. M. W., AGE 7 YEARS, TETRALOGY OF FALLOT

Paroxysmal supraventricular tachycardia with reversion to normal after intravenous digitalis.

A. Leads 1, 2, and 3, normal sinus rhythm, rate 125; pre operative.

B. Leads 1, 2, and 3, spontaneous aberration of QRS (lead 1), nodal rhythm with interference dissociation (lead 2), nodal rhythm and ST segment depression (lead 3); during anastomosis.

C. Leads 1, 2, and 3, nodal rhythm with upright P waves and short PR interval, rate 150, depression of ST segments leads 2 and 3; completion of anastomosis.

D. Leads 1, 2, and 3, paroxysmal supraventricular tachycardia, rate 300; chest closed.

E. Lead 2, gradual emergence of P wave to normal sinus rhythm after intravenous digitalis (Lanatoside C).

F. Lead 2, normal sinus rhythm, rate 130.

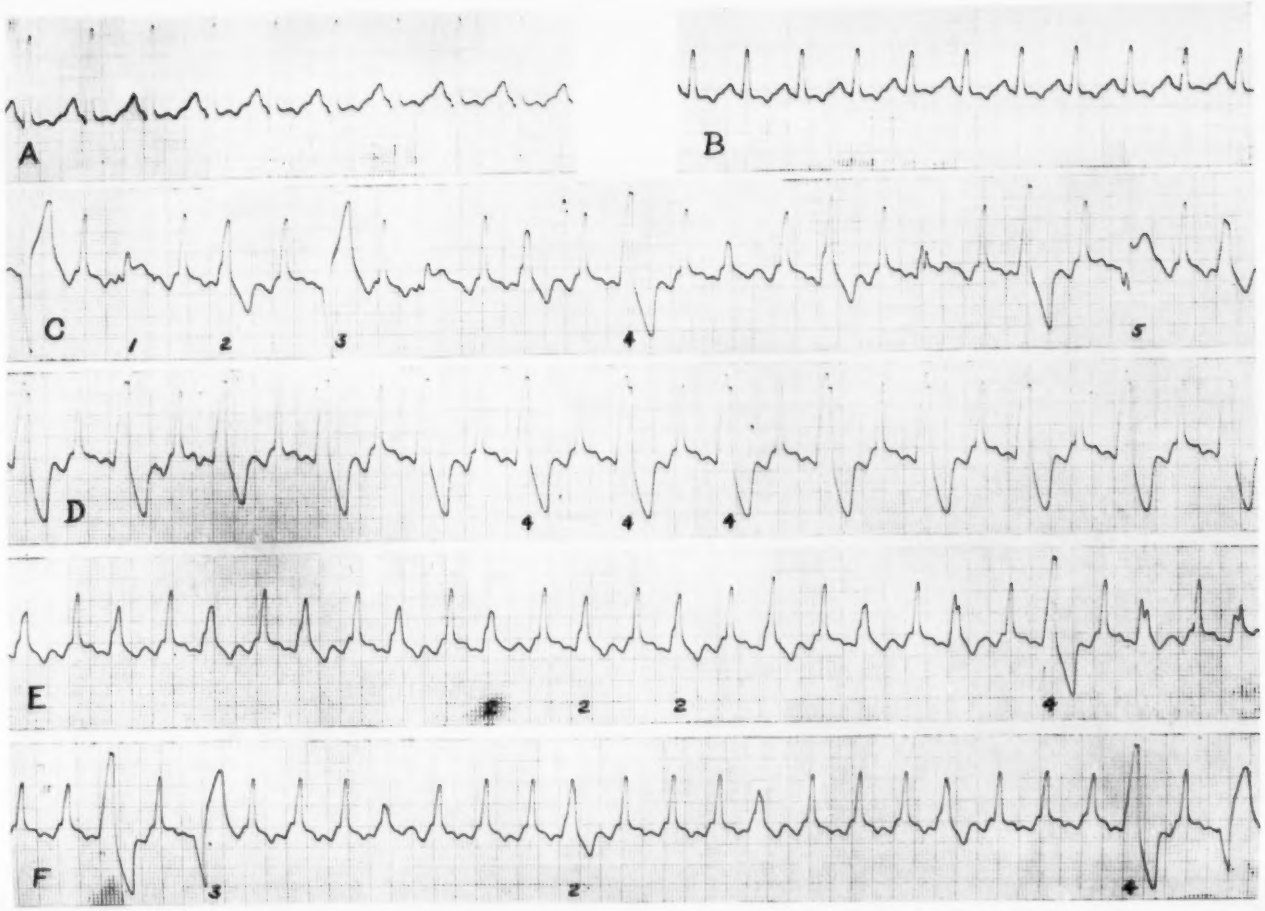


FIG. 4

QRS and consequently of the mean electrical axis of the heart (35). These changes occurred throughout all stages of operation and could not be associated with any particular event. They appeared at times to be cyclic as though varying with the phase of respiration and the position of the heart in the thorax; at other times, however, they appeared, disappeared, and reappeared without any apparent explanation. It is assumed that such variations in the form of QRS probably represent relatively minor changes of intraventricular conduction. Bundle branch block was observed only in the terminal cases, but was simulated in five additional instances by the superimposition of P waves on QRS during AV nodal rhythm (Fig. 5). ST segment and T wave changes occurred predominantly under circumstances indicating the probability of myocardial anoxia as a causative factor, once during paroxysmal tachycardia (Fig. 3), and in the remaining instances becoming most marked with the chest open and lung collapsed (Fig. 6) or just before release of the clamps after completion of the anastomosis.

Disturbances of conduction were infrequent, and their significance uncertain. It may be stated simply that such factors as autonomic imbalance and anoxemia are known to cause such changes as those observed.

In the terminal group were included seven children who died during anesthesia or operation, two children who experienced several episodes of cardiac asystole on the operating table and who died within 24 hours of cerebral thrombosis probably occurring during asystole, and one additional child whose operation was postponed after surviving what was thought to be a series of preterminal arrhythmias during anes-

FIG. 4. W. G., AGE 16 YEARS, TETRALOGY OF FALLOT

Ventricular premature systoles resulting from effect of cyclopropane, regular rhythm after changing to ether and oxygen. Lead 3.

A. Normal sinus rhythm; pre-operative.

B. Normal sinus rhythm; postoperative.

C. Ventricular premature systoles from multiple (5) foci; mediastinal dissection.

D. and E. Bigeminal rhythm with ectopic focus at first in one and then in the other ventricle.

F. Gradual subsidence of active arrhythmia after stopping cyclopropane, inverted P waves preceding QRS with normal PR interval.

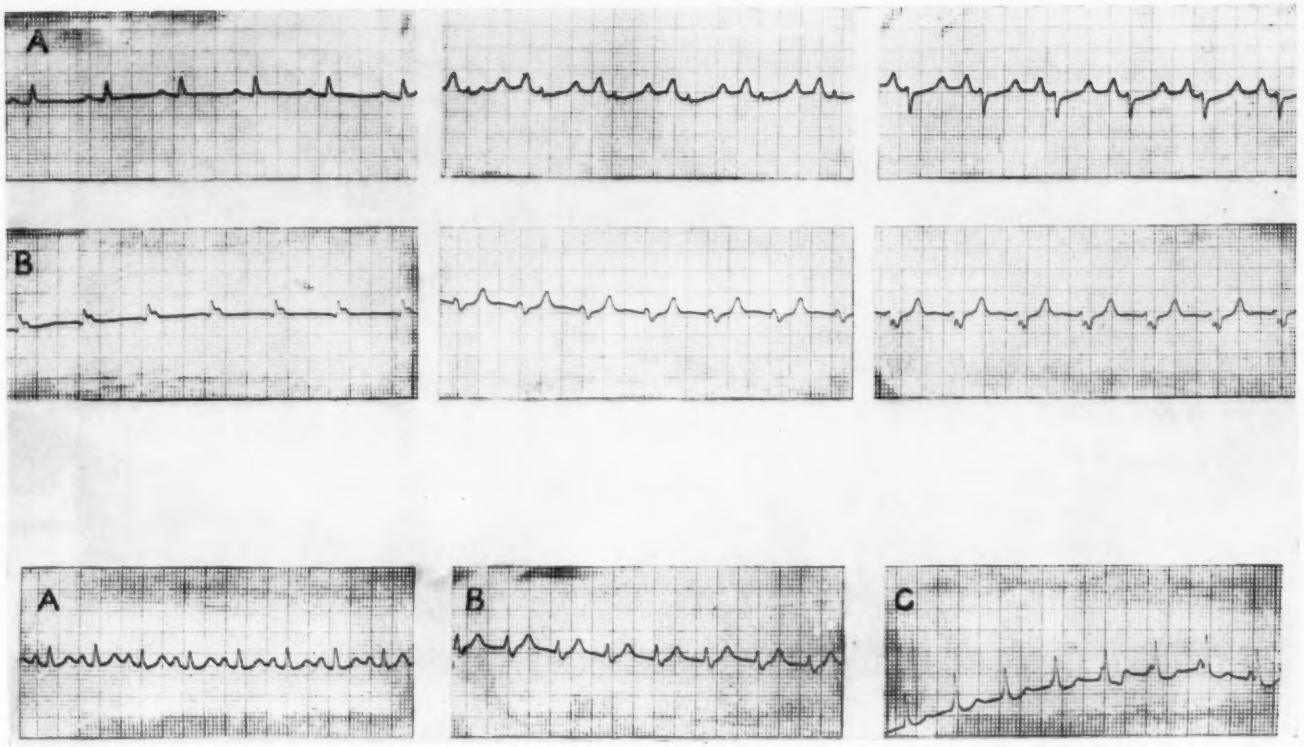


FIG. 5

thesia. Though this group is relatively small, certain differences of probable significance were observed between them and the larger control series.

The terminal cardiac mechanism in each of the seven cases was cardiac asystole (Fig. 8 and 9). It is interesting and probably of some importance that ventricular fibrillation occurred only once, and in this case long after death had already resulted from prolonged asystole (Fig. 9). Despite the fact that isolated cases of survival have been reported following long periods of cardiac arrest (1, 5), it was at first believed that the earliest onset of hypodynamic heart action marked the beginning of an irreversible terminal mechanism. The occurrence, however, of three patients surviving this period of asystole, while in no way decreasing the ultimate importance of such an event in this type of case, led to the newer belief that something might be done about it especially if any warning of impending danger might be foreseen. The records were carefully analyzed with this in mind, and certain observations of probable significance were noted.

In every case except one, sinus tachycardia with a rate of 150–200 preceded the onset of any other abnormality of the cardiac mechanism. While this incidence is significantly higher than in the control group, there is nothing sufficiently distinctive about it to forewarn of anything more serious to follow. Of much greater significance was marked bradycardia, either sinus or AV nodal, occurring in every case prior to terminal asystole. This form of bradycardia differed in several important respects from that occurring in the control series. The rate in the terminal group ranged from 23–50 per minute, while in the control group it was never less than 55 and in most cases was considerably faster. In five cases of the terminal group the bradycardia either

FIG. 5

FIG. 5. TWO CASES DEMONSTRATING SIMULATION OF BUNDLE BRANCH BLOCK, THE RESULT OF SUPERIMPOSITION OF P WAVES ON QRS DURING AV NODAL RHYTHM

Upper two records—M. C., age 18 years, pulmonary stenosis and possible single ventricle. Left axis deviation in the extremity leads (and left ventricular hypertrophy in the precordial leads). A. Leads 1, 2, and 3, normal sinus rhythm, rate 88; pre-operative. B. AV nodal rhythm; during anastomosis.

Lower record—W. B., age 11 years, probable tetralogy of Fallot. A. Lead 2, normal sinus rhythm, rate 125; pre-operative. B. Lead 2, AV nodal rhythm, rate 125; during anastomosis. C. Lead 3, emergence of P wave from QRS.

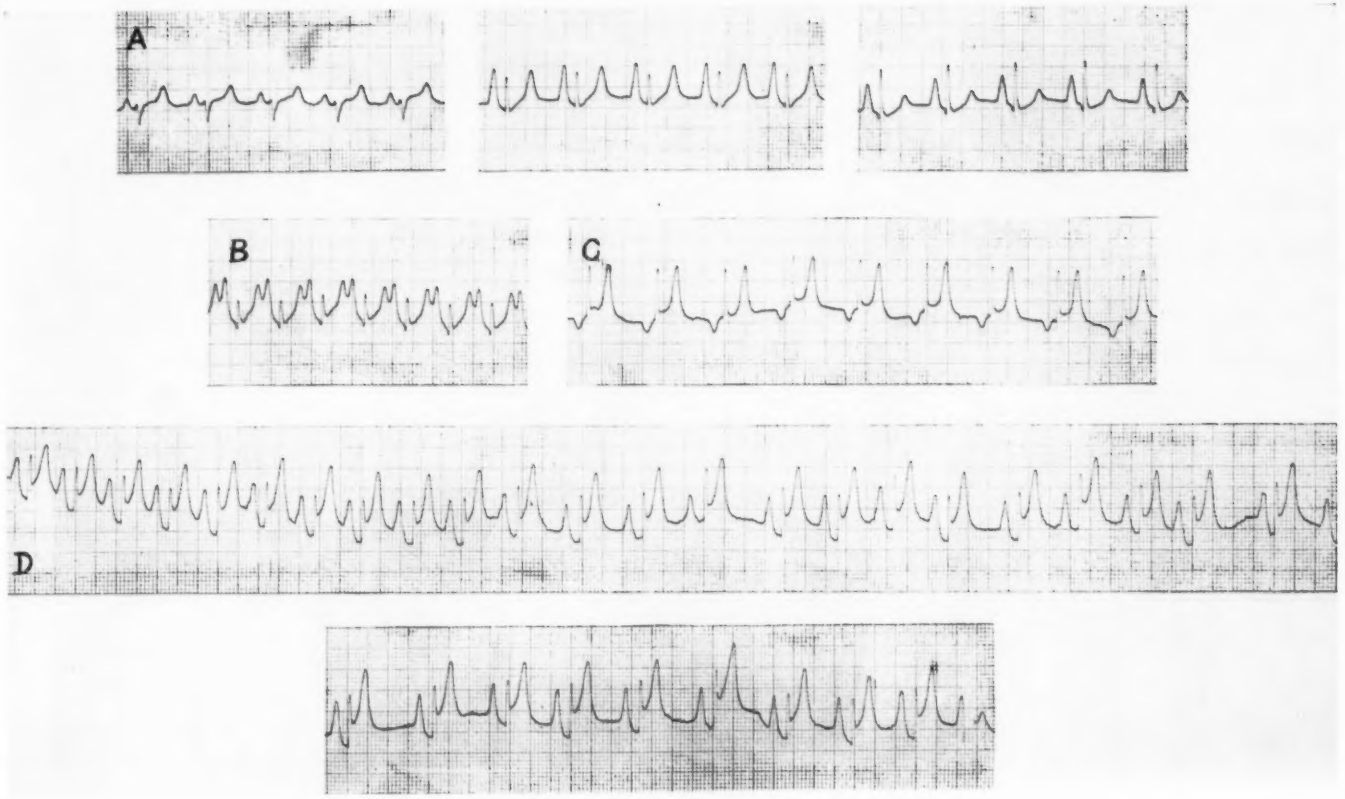


FIG. 6

occurred despite the administration of atropine or failed to revert to normal after atropine. In the control group, on the contrary, those with bradycardia invariably responded to the administration of atropine with an increase in heart rate, the only ones failing to respond already having a ventricular rate faster than during the preceding sinus rhythm. Of the nine children who died, only one-third (3 cases) proceeded to terminal asystole during the first episode of bradycardia (Fig. 8) while two-thirds (6 cases) had at least one and sometimes several episodes of bradycardia prior to the terminal event. It therefore seems evident that bradycardia, either sinus or nodal, with a rate of less than 50 per minute, and with failure to respond to the administration of atropine, constitutes a specific warning of impending terminal asystole. Other abnormalities of the cardiac mechanism were observed in the terminal group with sufficient frequency to be considered important evidence of cardiac damage and the accompanying danger of preterminal arrhythmias. These included complete bundle branch block in two cases, ventricular tachycardia in three cases, important ST segment deviation in three cases, complete AV dissociation in nine cases including two patients with auricular rhythm but absence of ventricular response, and sinus arrest in nine cases. The two latter abnormalities only occurred terminally and therefore could not be utilized as a danger signal in time to make use of prophylactic or therapeutic measures. Complete AV dissociation never developed during operation in those who survived but was present preoperatively in four children, three of whom survived operation and one of whom died after a clamp was placed on what was later discovered to be a single pulmonary artery.

From the data thus far available one can only speculate as to the probable mechanism of terminal arrhythmias occurring during anesthesia and operation in children with congenital heart disease and

FIG. 6

FIG. 6. C. B., AGE 5 YEARS, TETRALOGY OF FALLOT

Operation discontinued before doing anastomosis because of poor clinical condition of patient and evidence of progressive cardiac damage due probably to anoxemia.

A. Leads 1, 2, and 3, normal sinus rhythm, rate 85; pre-operative.

B. Lead 2, sinus tachycardia, rate 150.

C. Lead 2, nodal bradycardia, rate 88; mediastinal exploration (inverted P preceding QRS with short PR interval).

D. Lead 2, irregular sinus tachycardia (? sinus arrhythmia) after atropine, rate 83–135. Progressive ST segment elevation (normal after chest closure).

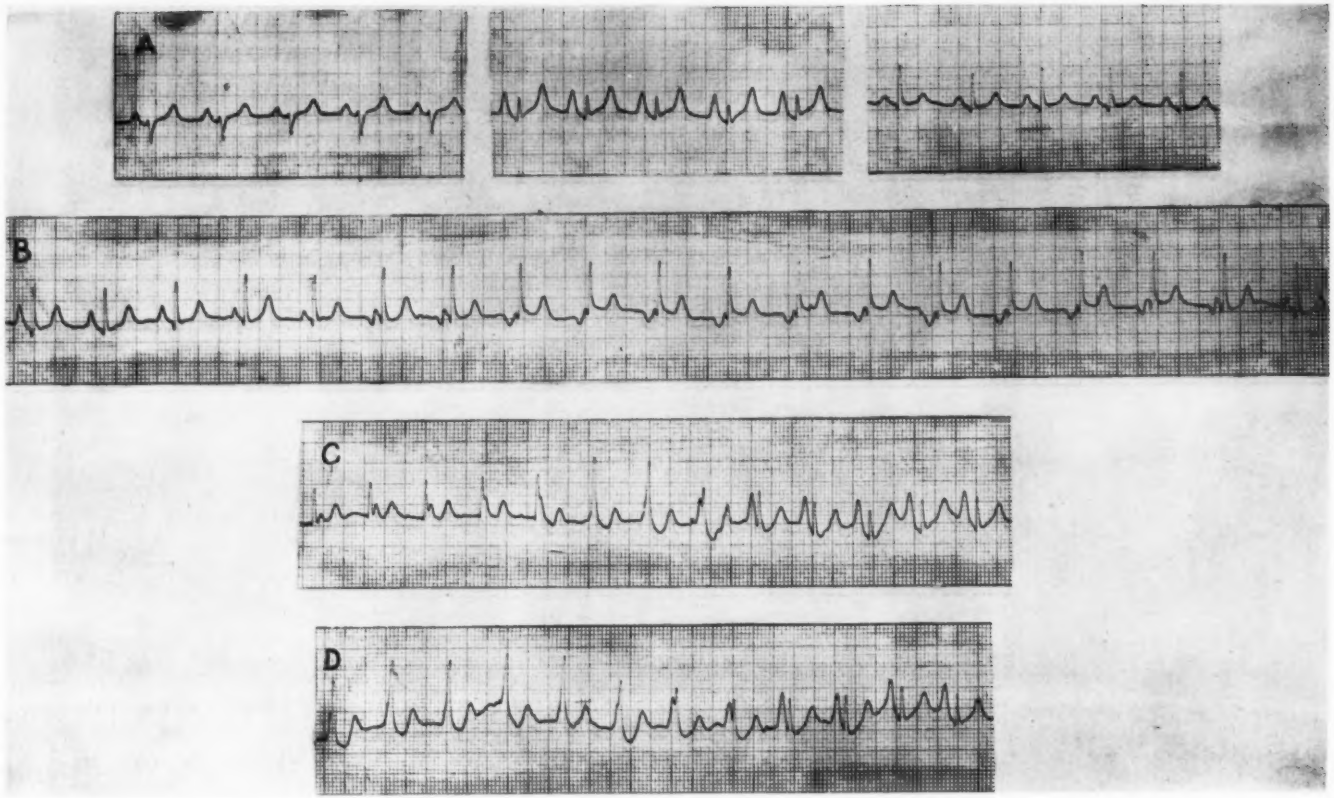


FIG. 7

cyanosis. There is much to suggest that anoxemia is a factor of considerable importance. Thus, death was known to have followed almost immediately the clamping of a single pulmonary artery in two instances and the only large collateral vessel in a third. By analogy with these three cases it seems reasonable to postulate a similar mechanism of terminal anoxemia in cases in which the only pulmonary circulation, and therefore oxygenation of the blood, depends during operation (as well as at all other times) on relatively limited collateral circulation which becomes seriously compromised when the lung is collapsed during thoracotomy. This would include patients with complete pulmonary atresia, truncus arteriosus without pulmonary arteries (essentially inoperable), and tetralogy of Fallot with a single pulmonary artery, of which types there was a high proportion in the terminal group (11 of 18 autopsied cases, 61%) (Table III). In support of this concept is the low average arterial oxygen saturation in the terminal group and the occurrence of other electrocardiographic abnormalities known to depend upon myocardial anoxia, as in coronary insufficiency with or without myocardial infarction. On the other hand, it is difficult in terms of this concept to explain a number of contrary facts including the following: (1) death during anesthesia when the arterial oxygen saturation may be high initially or may rise above the pre-operative level after induction; (2) frequent survival of patients with supposed complete pulmonary atresia (clinical diagnosis); (3) death of children with uncomplicated tetralogy of Fallot, and particularly those with a relatively high arterial oxygen saturation. It seems evident that, although anoxemia may be an important factor, there must be other factors acting adversely during anesthesia and operation in this type of patient. Among these may be listed vagal stimulation (17, 25), other imbalance of the autonomic nervous system (4), direct effect of the anesthetic agent on a sensitized myocardium (19, 20, 22), decreased

FIG. 7

FIG. 7. SAME PATIENT AS IN FIG. 6, SECOND ATTEMPT AT OPERATION WITH SUCCESSFUL COMPLETION OF ANASTOMOSIS

A. Leads 1, 2, and 3, normal sinus rhythm, rate 88; pre-operative.

B. Lead 3, transition of P wave—upright, diphasic, inverted—representing progressive variation in position of pacemaker.

C. and D. Progressive alteration in relation of P to QRS, auricles responding to sinus impulses, ventricles responding to AV-nodal impulses, auricular rate slightly faster than ventricular; mediastinal exploration.

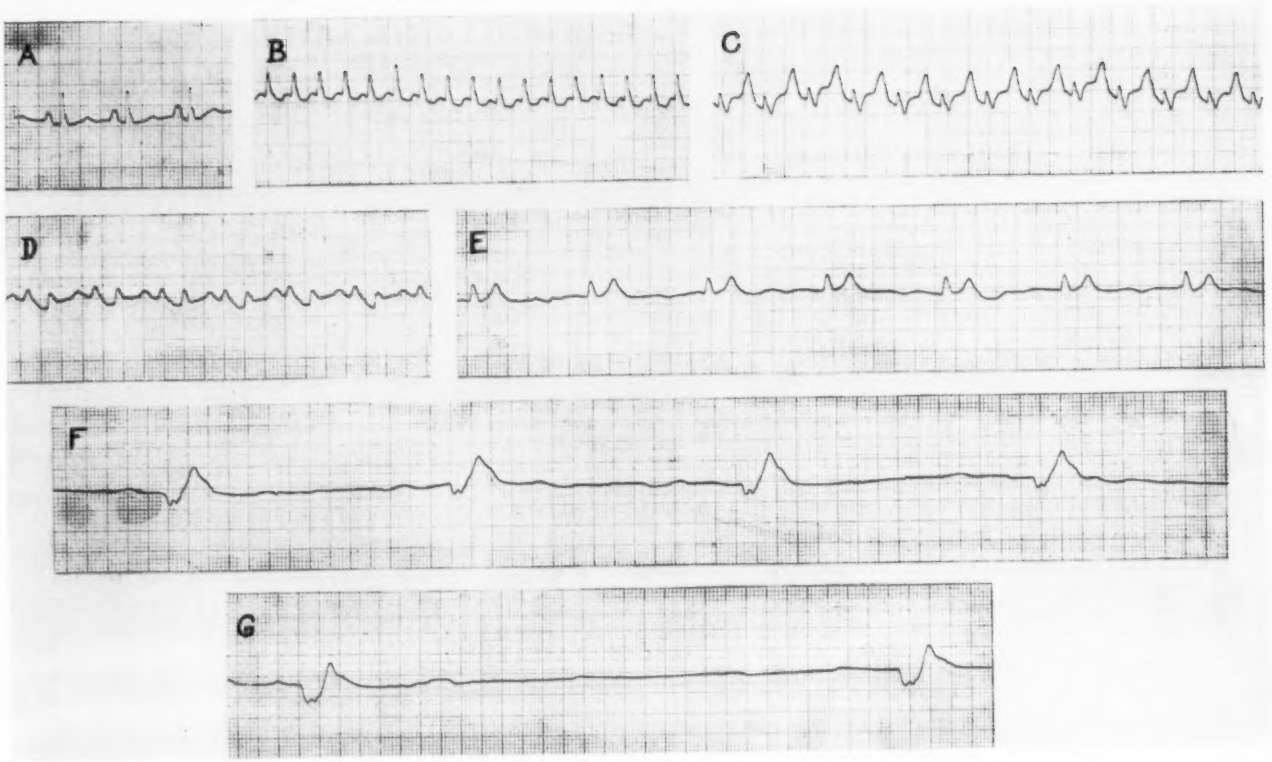


FIG. 8

cardiac output with positive endotracheal pressure (15), adrenal cortical insufficiency, potassium inhibition, and perhaps others. From the viewpoint of specific treatment it is obvious that exact knowledge of all of the factors contributing to death during anesthesia and operation is of the greatest importance. From the foregoing observations it can be justifiable only to point out certain possibilities. Further investigation will still be necessary to clarify many of the problems encountered in a study of this sort.

DISCUSSION

Before discussing the management of the important cardiac arrhythmias occurring during anesthesia and operation it is necessary to consider the general value of the electrocardiogram in the detection of significant disturbances of the cardiac mechanism. In the first place, the electrocardiograph is an extremely sensitive instrument for recording variations in the heart's action. This is demonstrated by the fact that arrhythmias have been detected in approximately 80% of the cases electrocardiographically (16) but in only 6.5% by ordinary clinical means (30). This does not mean, of course, that all of these arrhythmias are of clinical significance; relatively few are actually of anything more than academic interest. On the other hand, the heart under direct observation was on a number of occasions seen to dilate and stop mechanically at the same time that the electrocardiogram continued briefly at least to show regular electrical impulses of normal rate and fairly normal configuration. It was also observed that regular electrical activity of some type continued long after clinical death of the patient and complete mechanical asystole. This seems reasonable since electrical systole need not necessarily bear any direct relation to mechanical systole; and it indicates further that an electrocardio-

FIG. 8

FIG. 8. M. B., AGE 17 YEARS (PATIENT NUMBER 4, TABLE III)

Unexplained death before opening pleura. Lead 2.

A. Normal sinus rhythm, rate 94; pre-operative.

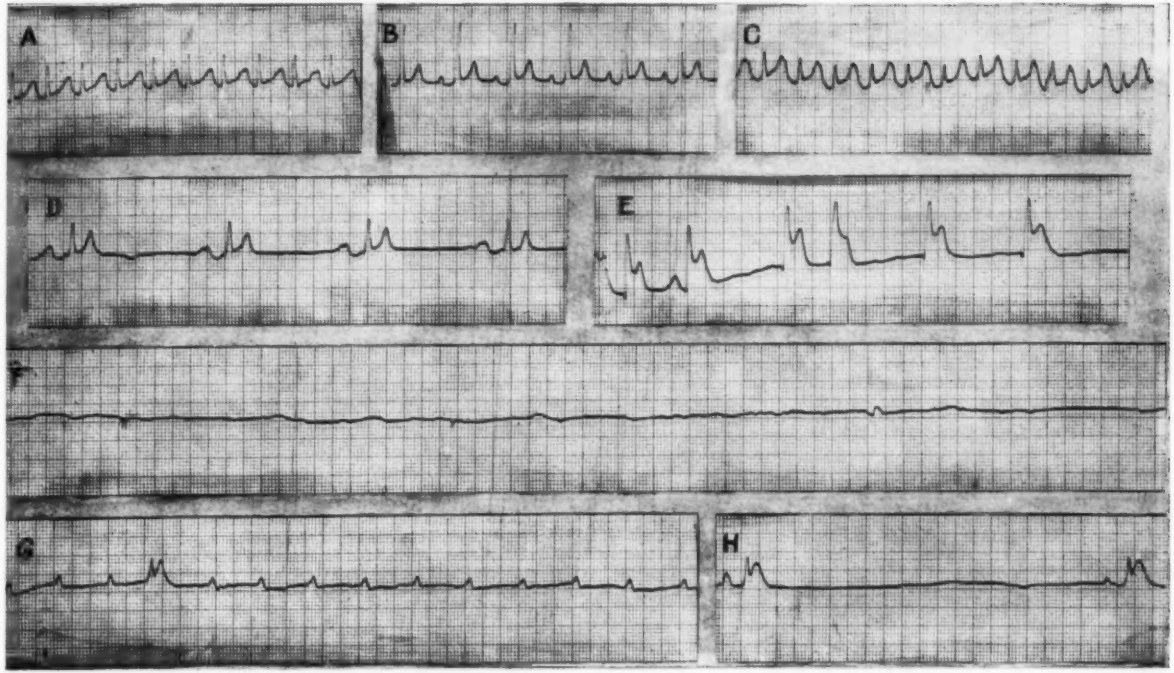
B. Paroxysmal supraventricular tachycardia, rate 250; skin incision.

C. Bundle branch block, or aberration of QRS by superimposed P wave.

D. Normal sinus rhythm.

E. Nodal bracycardia, rate 53, failure to respond to administration of atropine or adrenaline, slight aberration of intraventricular conduction.

F. and G. Sinus arrest, idioventricular rhythm, terminal complete asystole.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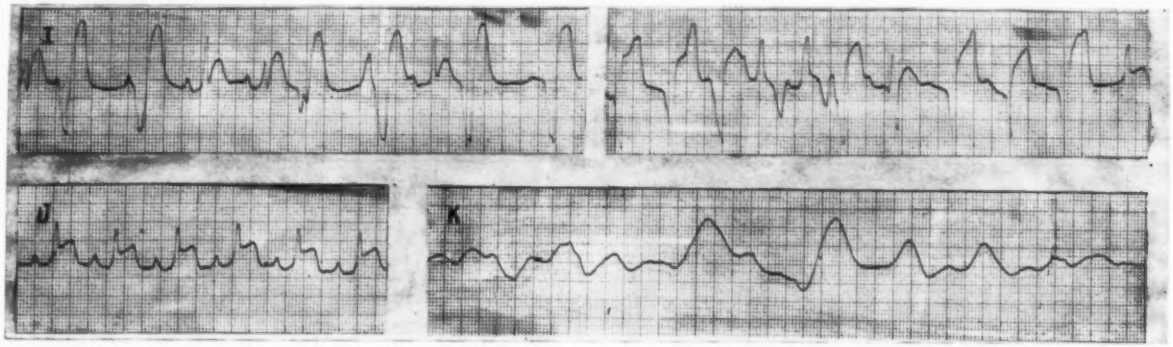

FIG. 9. B. L., AGE 8 YEARS (PATIENT NUMBER 13, TABLE III)

Preterminal and terminal cardiac mechanism during anastomosis after clamping single pulmonary artery. Lead 2.

A. Sinus or auricular tachycardia, rate 150, P wave superimposed on preceding T; during anaesthesia.
B. Normal sinus rhythm, rate 100; chest incision.
C. Sinus or auricular tachycardia with ST segment elevation.
D. Sinus bradycardia, rate 38; during anastomosis, after adrenaline and coramine.
E. Sinus arrest, irregular idioventricular rhythm.
F. Complete asystole and clinical death (cardiac massage).
G. Auricular rhythm without ventricular response; after calcium chloride.
H. Slow sinus rhythm, rate 14, with ST segment elevation and short QT interval.
I. Multiple ventricular premature systoles.
J. Sinus rhythm with marked ST segment elevation.
K. Ventricular fibrillation; approximately one hour after clinical death during asystole.

TABLE III

TIME	AGE	DIAGNOSIS	O_2 SATURATION	COMMENTS
			per cent	
Anesthesia				
1. M. C. (F)	22 yrs.	—	66.8	Survived anesthesia
Opening chest				
2. N. Q. (M)	2½ yrs.	Pulmonary atresia	42.0	
3. J. P. (F)	5 yrs.	Pulmonary atresia	42.4	
4. M. B. (F)	17 yrs.	Pulmonary stenosis, valvular, patent foramen ovale	72.2	Unexplained death before chest opened
Mediastinal dissection				
5. B. C. (M)	4 yrs.	—	36.5	
6. M. K. (M)	7 yrs.	Tetralogy	40.1	
7. G. B. (F)	2 yrs.	Single ventricle	26.3	
8. I. S. (M)	7 yrs.	Tetralogy, single pulmonary	65.2	Clamp on single pulmonary
9. L. W. (M)	2½ yrs.	Tetralogy	—	
During anastomosis				
10. C. D (F)	8 yrs.	Tetralogy	29.7	
11 D. K. (M)	5 yrs.	Tetralogy	41.9	
12. H. G. (F)	26 yrs.	Pulmonary stenosis, tricuspid atresia	38.4	
13. B. L. (F)	8 yrs.	Tetralogy, single pulmonary	34.7	Clamp on single pulmonary
14. S. S. (F)	2 yrs	Truncus arteriosus, no pulmonaries	36.0	Clamp on single collateral
15. S. S. (F)	3 yrs.	Tetralogy	—	
After completion of anastomosis				
16. D. C. (M)	8 yrs.	—	46.4	
17. D. B. (M)	14 yrs.	Pulmonary stenosis, valvular, single ventricle	64.2	Complete heart block acute dilatation
18. P. N. (M)	7 mo.	Truncus arteriosus, no pulmonaries	13.4	
19. K. M. (F)	2½ mo.	Pulmonary atresia	17.5	
20. C. F. (F)	23 mo.	Pulmonary atresia	7.5	
21. R. D. (F)	4½ mo.	Pulmonary atresia	18.2	
22. B. W. (F)	4 yrs.	Tetralogy	52.8	Operation completed, cerebral thrombosis during asystole
23. I C. (F)	3½ yrs.	—	38.7	Operation completed, cerebral thrombosis during asystole
24. C. H. (M)	15 yrs.	Tetralogy, anomalous venous return	63.0	Anomalous venous return

graphic record, while of considerable value, does not completely replace direct observation in the detection of serious abnormalities of the heart's action during thoracic surgery. Somewhere between these

TABLE IV

Important Arrhythmias: Pathogenesis and Management

	CAUSE	DANGER	TREATMENT
Ventricular premature systoles	Cyclopropane	Ventricular tachycardia and fibrillation	Stop cyclopropane, increase oxygen
Paroxysmal tachycardia	?	Congestive failure Peripheral collapse and thrombosis	Vagus stimulation (carotid sinus pressure) Intravenous digitalis
Nodal or sinus bradycardia	Vagal stimulation (direct or anesthetic)	? preterminal	Atropine
Nodal or sinus bradycardia below 50, no response to atropine, and other evidence of anoxemia	Anoxia Vagal stimulation Anesthetic poisoning of respiratory enzymes Decrease cardiac output Potassium inhibition Adrenal cortical insufficiency, etc.	Terminal asystole	Inflate lungs Increase oxygen in anesthetic mixture Intravenous oxygen Transfusion of oxygenated blood Cytochrome Cardiac massage ? Cardiac stimulants, etc.
Sinus or nodal tachycardia Auricular or nodal premature systoles Minor aberration of QRS		Arrhythmias of no clinical significance	

two extremes lies the real importance of the electrocardiogram during anesthesia and operation: the early detection of abnormalities of the cardiac mechanism which indicate serious myocardial damage and which might progress to a terminal arrhythmia. It is hoped that

such knowledge of the heart's action might lead to intelligent and effective management with the resultant saving of lives which might be lost otherwise.

The first problem encountered in a study of this sort is the determination of just what constitutes a significant abnormality of the cardiac mechanism. These may be classified as follows:

Electrocardiographic:

I. Major disturbances of heart rate
   A. Ectopic tachycardia
   B. Sinus or AV nodal bradycardia of extreme degree, especially with failure to revert to and remain normal after atropine

II. Evidence of anoxemia
   A. ST segment and T wave abnormalities
   B. Major disturbance of intraventricular conduction (bundle branch block)
   C. Complete AV dissociation (exclusive of interference dissociation)
   D. Sinus arrest

III. Ectopic arrhythmias with potential danger of ventricular fibrillation
   A. Ventricular premature systoles
   B. Ventricular tachycardia

Direct observation:

I. Dilatation and mechanical asystole

II. Increasing cyanosis

III. Signs of cerebral damage (in absence of occlusion of innominate or carotid artery)

IV. Fall in blood pressure without hemorrhage or significant change in heart rate

There appears to be a very wide range of heart rate within which normal cardiac efficiency and normal circulatory dynamics may be maintained. Even the extremes of sinus bradycardia and tachycardia seldom exceed this wide margin of safety. It seems probable that under ordinary circumstances there is little danger of congestive heart failure or peripheral vascular collapse with subsequent vascular thrombosis (cerebral or at the anastomotic site) until the heart rate

exceeds 180–200, and then only when the tachycardia is maintained over a fairly long period of time (probably several hours or more). This circumstance apparently only occurs with an ectopic tachycardia such as paroxysmal auricular or nodal tachycardia (Fig. 3), auricular flutter, or auricular fibrillation, and constitutes an indication for prompt and adequate treatment. Effective treatment consists primarily of vagus nerve stimulation, either reflexly by carotid sinus or ocular pressure, or directly by specific medication such as the administration of mecholyl. Since mecholyl and related drugs have several unpleasant side-effects and at best may not be given without significant danger, and because carotid sinus pressure alone is frequently ineffective, the intravenous administration of a purified glycoside of digitalis appears to be the treatment of choice. This may be given as lanatoside C or digitoxin in a dosage of approximately 30 micrograms per kilogram of body weight. Atropine, by preventing the effects of vagal stimulation, may tend to perpetuate this type of arrhythmia at least until the effects of its previous administration have subsided. This constitutes one possible objection to the routine preoperative use of atropine especially in individuals who give a history of paroxysmal tachycardia or who may be predisposed in any way to the development of such an arrhythmia. Bradycardia, on the contrary, usually responds to atropine by a prompt reversion to normal sinus rhythm or sinus tachycardia. Consequently, when the heart slows or when nodal rhythm with or without interference dissociation occurs as a result of the anesthetic or of vagal stimulation, the administration of atropine is indicated. When the ventricular rate is less than 50 per minute and when the bradycardia fails to revert to normal or tends to reoccur after the administration of atropine, the danger of a terminal cardiac arrhythmia may be considered to be imminent and the institution of well-considered therapeutic procedures urgent.

Until the exact pathological physiology of these preterminal arrhythmias is known, treatment must remain upon a more or less empirical basis. From the observations of the present study, however, a number of suggestions for specific therapy and for further investigation may be made. Thus, there is evidence that severe anoxemia may be a factor of considerable importance in the development of a serious degree of myocardial depression (13). Further detailed information on this

problem should be derived from a correlation of electrocardiographic data with direct oximeter determinations of arterial or capillary oxygen saturation during anesthesia and operation. Until such a study is made it would seem reasonable to assume that pulmonary collapse and the unavoidable interruption of collateral circulation incident to thoracotomy and mediastinal dissection must almost certainly reduce an already decreased arterial oxygen saturation to dangerously low and perhaps lethal levels despite the original slight increase which may occur during induction (12). If such is the case, a number of therapeutic procedures may be considered. The first and simplest would be to increase the availability of oxygen. However, under the circumstances described, breathing even 100% oxygen under positive pressure will probably help little if at all because of the marked reduction of pulmonary circulation which is present until after the newly created systemic-pulmonary anastomosis has been opened and the collapsed lung re-expanded. It follows that even before completion of the anastomosis periodic inflation of the collapsed lung might be of benefit by making the oxygen in the anesthetic mixture more available to the pulmonary circulation, particularly in individuals considered to be especially vulnerable from the standpoint of anoxia. (The frequency of re-expansion of the lung could be determined perhaps by oximeter readings.) An alternative method of making oxygen available, but one which has not proved to very practicable as yet, is to administer gaseous oxygen intravenously (34) or to transfuse the patient with oxygenated blood (14). An entirely different solution to the problem is offered in the use of respiratory enzymes and related materials such as cytochrome C (23), the B vitamins (24), and perhaps others, for increasing tissue utilization of oxygen and possibly helping the patient thereby to survive a relatively brief period which might otherwise terminate fatally. It must also be remembered that tissue anoxia may be stagnant or anemic rather than, or in addition to, anoxic. The factor of anemia is not uncommon, particularly in infants, and should be corrected preoperatively by proper methods such as the administration of iron and small repeated blood transfusions. During anesthesia and operation stagnant anoxia, which may result from a failing circulation and which may in turn further depress the heart and circulation, should be benefited by the action of cardiac stimulants such as epi-

nephrine and digitalis. Adequate attention must be given, in addition, to other factors known to be important in thoracic surgery, both cardiac and non-cardiac, including the maintenance of an adequate airway, control of the movement of the lung and mediastinum, the prevention of too great a degree of dependency of the good lung during open pneumothorax, the prevention of vascular obstruction by improper retraction, and others (2).

Should the heart dilate and stop, two questions must be answered: (1) What methods must be used for immediate resuscitation? and (2) If the heart can be revived, what should be done about continuing or not with operation? The subject of resuscitation of the failing heart is still a controversial one, although certain procedures are generally accepted and certain others warrant further consideration (1, 5, 6). There appears to be a sound basis for the immediate institution of cardiac massage—not just plain "squeezing" of the heart—but the rhythmical application of external force to the ventricles in a direction from apex to base in order to simulate as closely as possible the normal action of the heart and thereby to maintain at least temporarily an adequate circulation (5). It must be remembered also that the maintenance of artificial respiration with a high concentration of oxygen is also necessary throughout this entire period. Manual massage probably accomplishes little more than the artificial maintenance of the circulation until such time as the heart can resume its own rhythmical action either spontaneously or more often with the help of other supportive and stimulative measures. The intracardiac injection of epinephrine has been one of the most widely recommended procedures (5, 7, 27), but there remains a great deal of controversy about the advisability of its use. Its effectiveness has been proclaimed by some and disclaimed by others. The danger of precipitating fatal ventricular fibrillation especially during cyclopropane anesthesia has been emphasized many times (19, 20, 22) and cases cited in which this was the "probable" cause of death. It is to be noted, however, that electrocardiographic evidence of this cardiac mechanism as a cause of death has been lacking in most human cases and, further, that in the present study ventricular fibrillation never occurred even after the administration of large amounts of epinephrine. This should not be considered final proof against the theory of cyclopropane sensitization of the heart to epi-

nephrine and the resulting danger of ventricular ectopic arrhythmias (19, 22). It may indicate simply that such sensitization does not occur in this particular type of case, in which severe anoxia may act as a general cardiac depressant instead of inducing localized regions of increased irritability, as in diseases of the coronary arteries. The observations cited in this study, as well as those of other recent publications (13, 21, 29) tend to support such a concept. Although it still remains a matter of some difference of opinion, it seems reasonable to state, for the present at least, that the use of epinephrine and other cardiac stimulants is of questionable and poorly defined value. It is likely that, although they may increase the force of contraction when the heart is still beating, however feebly, they will not often initiate contractions after they have already ceased. Greater value might be expected from the administration of a longer acting specific cardiac stimulant, such as digitalis, or by supplying the heart with essential materials for energy production, such as available oxygen, respiratory enzymes, electrolytes, etc., at the same time that the circulation is maintained by manual massage or the rhythmical stimulation of an artificial pacemaker.

Should normal rhythmicity of the heart be re-established following the occurrence of cardiac asystole or other serious preterminal arrhythmia, the difficult question of continuing operation must be decided. It is not possible, nor is it intended, to attempt making any final answer at the present time, for the decision must be made on the merits of each individual case. However, several observations are worthy of mention. It should be noted, for example, that few children ultimately survive the occurrence of pre-terminal arrhythmias as observed in this study. Only three children of the entire group survived operation, and of these two died within 24 hours of cerebral thrombosis which probably occurred during cardiac asystole. Thus, only one child ultimately survived, and in this instance no actual surgery was performed since the arrhythmia occurred during anesthesia and operation was indefinitely postponed. It seems apparent, therefore, that regardless of proceeding with operation or not, ultimate survival after the occurrence of a preterminal arrhythmia is not likely even after the restoration of apparently normal heart action. It is possible, however, that newer methods of treatment may favorably affect this

practically hopeless outlook. Considering the problem from another point of view, to subject a child with congenital heart disease and cyanosis to exploratory thoracotomy with the attendant disruption of a variable but significant number of collateral vessels, without completing the anastomosis for which the operation was intended, does a great deal of harm and frequently results in death. In fact, the mortality rate in such cases is as high or higher than in the group of children in whom the entire operation has been completed. Therefore, unless operation is discontinued or postponed for a specific reason, or unless it can be attempted again in the near future with at least equal or perhaps greater safety, considerable thought must be given to the advisability of discontinuing or of proceeding with operation after the occurrence of the type of arrhythmia under discussion. Frequently the attitude of "nothing to lose and everything to gain" seems justified. Also, it may be that with the development of newer methods of treatment, based upon such principles as those suggested, a more satisfactory answer may be found for this entire problem.

Another type of arrhythmia which requires consideration is the occurrence of frequent premature systoles particularly of ventricular origin. These appear to be due in the great majority of instances to the direct action of cyclopropane on the heart (Fig. 9), and have been considered, correctly or not, to constitute a prefibrillary arrhythmia (19, 20, 22). Despite the fact that ventricular fibrillation was never observed in this series, and despite the lack of electrocardiographic evidence to confirm ventricular fibrillation as a major cause of immediate anesthetic death in humans, it appears to be a simple and reasonable measure of security to stop cyclopropane as an anesthetic agent and continue with ether and oxygen in the presence of multiple ventricular premature systoles or ventricular tachycardia. Such a procedure has resulted in the disappearance of the former in every instance, the latter only having occurred in the terminal group. A number of other means have been suggested for preventing ventricular fibrillation. These include the use of barbiturates and other drugs (3) and the local application or parenteral administration of local anesthetics such as procaine (9, 18). There would appear to be little use for this type of therapy except perhaps in ventricular tachycardia, though even in this arrhythmia the danger of ventricular fibrillation

is not great in patients with anoxemia and evidence of cardiac depression. Methods have been tried and recommended also for the management of actual as well as imminent ventricular fibrillation (6).

The other disturbances in the cardiac mechanism observed during this study are largely of academic interest and do not seem to have any immediate clinical significance. This applies particularly to the various forms of nodal rhythm. Of particular interest are the changes which occur in the configuration of QRS without evidence of bundle branch block, primarily those involving gross changes in the position of the mean electrical axis of QRS. This problem is the subject of further investigation, the results of which will be published separately (35). However, certain comments may be made here on the basis of present information. The position of the mean electrical axis in the extremity lead electrocardiogram until recently has been considered evidence of hypertrophy of one or the other ventricle. Even now it is not generally appreciated that other factors, such as the position of the heart in the thorax, may influence even more strongly the configuration of the ventricular deflections particularly in the extremity leads. In the cases under consideration, the position of the heart being relatively fixed and changes in ventricular preponderance obviously not being a factor, a third influence must be considered, namely changes in intraventricular conduction exclusive of those producing gross bundle branch block. The clinical significance of these changes is not at all certain, although they have been described previously in infectious diseases (28) presumably as the result of toxic myocarditis, and in these surgical cases may represent additional evidence of myocardial damage due to anoxemia. It is of interest and probably of some significance that the three children in whom the most marked changes in QRS occurred all had more complicated malformations than a simple tetralogy of Fallot; that all three had severe congestive heart failure following the systemic-pulmonary anastomosis; and that two died in less than one year after operation, the third surviving perhaps only because of ligation of her artificial ductus.[1] Whatever the pathogenesis, the observation that gross alterations in the form and direction of QRS may occur without changes in the position of the heart or changes

[1] These three cases will be reported in further detail elsewhere, the first two by Ziegler (35), the third by Dr. William Adams.

in the relative mass of either ventricle and without gross abnormalities of intraventricular conduction, such as bundle branch block, is of considerable importance among the fundamental principles upon which the interpretation of the electrocardiogram is based.

CONCLUSIONS

Electrocardiograms were recorded practically continuously during anesthesia and operation in 175 children with congenital heart disease and cyanosis. From this study the following observations concerning the occurrence, significance, and management of abnormalities of the cardiac mechanism were made:

1. Arrhythmias of some sort occurred in approximately 80% of the entire group of patients. These varied from simple variations of rate to complex terminal mechanisms and included many forms of active and passive ectopic arrhythmias which occurred throughout all phases of anesthesia and operation.

2. The most common abnormality was the group of arrhythmias resulting from depression of the normal pacemaker with supercedence of some center of lower rhythmicity, usually the atrio-ventricular node. This abnormality of the cardiac mechanism was usually benign and in most instances reverted to normal, either spontaneously or following the intravenous administration of atropine.

3. Arrhythmias resulting from increased cardiac irritability, including primarily ventricular premature systoles and paroxysmal auricular or AV nodal tachycardia, occurred in slightly more than 10% of the patients; and, although these may be considered generally to be relatively benign disorders of the cardiac mechanism, under the circumstances of cyclopropane anesthesia and intrathoracic operation in a child with an abnormal heart and anoxemia they were treated with certain potential dangers in mind. Ventricular premature systoles were believed to constitute a possible precursor to a much more serious ventricular tachycardia or fatal ventricular fibrillation and responded satisfactorily in all instances to stopping cyclopropane and continuing with ether and oxygen or oxygen alone. Paroxysmal tachycardia, especially with a long continued rapid ventricular rate, was considered potentially hazardous because of the possibilitites of congestive heart failure or peripheral vascular collapse, with resulting venous or arterial

thrombosis, and was treated immediately by vagus stimulation, usually in the form of the intravenous administration of digitalis in full dosage.

4. Spontaneous changes in the form of the ventricular deflections, detectable only in the electrocardiogram, appeared to have no immediate significance from the surgical viewpoint, but seemed to occur more frequently in children with more complicated cardiovascular malformations than the simple tetralogy of Fallot and whose postoperative course was commonly complicated by the occurrence of congestive heart failure.

5. The terminal cardiac mechanism was recorded in seven children who died during operation; and in each instance the final event was sinus arrest with complete cardiac asystole. On the basis of a careful analysis of the entire electrocardiographic record it was believed that in practically every instance terminal asystole was preceded by one or more specific preterminal phenomena including the following: sinus or AV nodal bradycardia with a rate of less than 55 per minute and either failing to revert to normal or recurring after the administration of adequate amounts of atropine; complete AV dissociation with idioventricular rhythm; ventricular tachycardia; complete bundle branch block; and other electrocardiographic changes interpreted as evidence of myocardial anoxia. Other evidences of hypodynamic heart action with impending terminal asystole included: falling blood pressure, not the result of hemorrhage or significant change in heart rate; progressive decrease in arterial oxygen saturation; and mechanical dilatation of the heart with asystole (occasionally with a normal electrocardiogram).

6. Evidence was given for believing that the terminal cardiac mechanisms are manifestations of myocardial depression as a result of anoxia. On the basis of this assumption treatment should be directed logically toward the correction of anoxia in all of its characteristic manifestations, including primarily the provision of available oxygen to the tissues and support for the failing heart and circulation. The value and the limitations of specific procedures were discussed. Although it is not possible at present to determine at what point the preterminal cardiac mechanism becomes irreversible, it seems certain that the earlier specific treatment is instituted the more likely it will be to result successfully; and, as in many other circumstances, prevention is more important than any treatment.

7. It is of significance that ventricular fibrillation never occurred as a cause of death even following the injection of epinephrine during cyclopropane anesthesia, thus providing further indirect evidence for the belief that anoxemia is a myocardial depressant. It seems apparent that epinephrine may be given with relative safety in the conditions of this study. It is probably true, however, that the administration of this drug is of little if any value in initiating cardiac contractions after they have already ceased.

8. Some indication has been given that digitalis may be of great value in maintaining normal cardiac function during anesthesia and operation, especially in selected patients. Additional investigation will be necessary to support this as well as certain other concepts encountered in this study.

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ADDENDUM

Since the completion of this electrocardiographic study, a continuous, systemic, arterial oxyhemoglobin concentration record was made by the method of Hartman, et al.,[1] during operation on a twenty-four year old patient with tetralogy of Fallot and functional complete pulmonary atresia. This case will be reported in further detail elsewhere but certain observations should be mentioned in connection with this study. These include the following:

1. The spontaneous occurrence of "hypodynamic heart action" with fall in blood pressure, imperceptible pulse and progressive decrease in oxygen saturation immediately following induction of anesthesia.

2. Beneficial but transient effect of epinephrine as evidenced by a return of oxygen saturation to the pre-anesthetic level.

3. Immediate and prolonged beneficial effect of a sub-digitalizing amount (two-thirds of the calculated dose) of intravenous digitalis as evidenced by systemic arterial oxygen saturation, blood pressure and heart action.

4. Maintenance of constant oxygen saturation in the face of open pneumothorax with its attendant complete atelectasis and with clamping of the pulmonary artery.

5. Immediate post-operative rise of oxygen saturation to normal after releasing the clamp at the anastomotic site.

It will be seen that these observations support, in part, the principles

[1] Hartman, F. W., Behrmann, V. G., and Chapman, F. W. Photo-electric Oxyhemograph; a continuous method for measuring the oxygen saturation of the blood. Am. J. Clin. Path., 18: 1–13, Jan. 1948.

previously mentioned regarding the relationship between cardio-circulatory failure and anoxemia. It is evident also on the other hand that oxygen saturation in the systemic blood need not necessarily decrease as the result of collapse of a lung and the disruption of collateral circulation. The results of this single study confirm the need for further observation of this sort which should contribute significantly to the solution of many of the problems encountered.

OBSERVATIONS ON THE EFFECTS OF FOLIC ACID ANTAGONISTS, FOLIC ACID, LIVER EXTRACT AND VITAMIN B_{12} ON EMBRYONATED EGGS[1]

A Preliminary Report

PHILIP F. WAGLEY[2] AND HERBERT R. MORGAN[3]

Received for publication June 14, 1948

This is a preliminary report of observations made on embryonated eggs following injections of three folic acid antagonists (1, 2), folic acid, purified liver extract and vitamin B_{12}.

Six to 8-day old chick embryos were inoculated via the yolk sac with three folic acid antagonists (4-amino-pteroylglutamic acid, N^{10}-methyl-pteroic acid and methyl-4-amino-pteroylglutamic acid)[4] alone or with folic acid (synthetic pteroylglutamic acid),[4] purified antipernicious anemia liver extract, or vitamin B_{12}[5] in the amounts indicated in the table. All substances except the liver extract were dissolved in distilled water. The embryos were incubated at 35°C. All deaths occurring in the first 48 hours were considered post-traumatic and discarded from the study. Yolk sacs were fixed in 10 per cent acetic acid Zenkers solution and microscopic sections were stained with eosin-methylene blue.[6]

The findings are recorded in Table I. Embryonated eggs injected with 4-amino-pteroylglutamic acid in amounts of 0.005 mg. showed a

[1] From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts. Aided by a grant from the National Foundation for Infantile Paralysis.

[2] Research Fellow of the American College of Physicians.

[3] Senior Fellow in Medical Sciences, National Research Council.

[4] Through the courtesy of the Lederle Laboratories, Pearl River, N. Y. the following materials were provided: folic acid as synthetic pteroylglutamic acid; 4-amino-pteroylglutamic acid (Lot # 7-7843C); N^{10}-methyl-pteroic acid (Lot # 7-7623A), and methyl-4-amino-pteroylglutamic acid (Lot # 7-8185).

[5] Vitamin B_{12} was provided through the courtesy of Dr. A. Gibson of Merck & Co., Inc., Rahway, New Jersey.

[6] The authors are indebted to Miss Lillian M. Leavitt of the Mallory Institute of Pathology for preparing the microscopic sections.

TABLE I

Effect of Folic Acid Inhibitors on Chick Embryos

SERIES	DRUG	DOSE	AGE AT INOCULATION	SURVIVAL TIME IN TERMS OF DAYS OF AGE									APPEARANCE OF YOLK SAC BLOOD ISLETS
				6	7	8	9	10	11	12	13	14	
			days										
1	4-amino-pteryoyl-glutamic acid	0.005 mg.	8			5/5*	5/5	5/5	5/5	3/5	1/5	0/5	Diminution in size and number of blood islets. Pyknosis, karyolysis karyorrhexis of nuclei
2	4-amino-pteroyl-glutamic acid	0.005 mg.	8			3/3	3/3	3/3	3/3	2/3	2/3	0/3	Same as Series 1
	Vitamin B_{12}†	0.005 mg.											
3	4-amino-pteroyl-glutamic acid	0.005 mg.	7		13/13	13/13	13/13	11/13	6/13	0/13			Same as Series 1
	Liver extract‡	3.75 units											
4	4-amino-pteroyl-glutamic acid	0.005 mg.	7		16/16	16/16	16/16	16/16	15/16	12§/16	11/16	10/16	Slight diminution in cellularity of blood islets
	Folic acid‡	12.5 mg.											
5	N^{10}-methyl-pteroic acid	20 mg.	6	8/8	8/8	8/8	7/8	6/8	4/8¶	4/8‖			Normal
6	Methyl-4-amino-pteroylglutamic acid	0.01 mg.	8			11/11	11/11	11/11	11/11	11/11	7/11	6/11	Diminution in size and number of blood islets. Fragmentation of nuclei
7	Methyl-4-amino-pteroylglutamic acid	0.01 mg.	8			12/12	12/12	12/12	12/12	11/12	10/12	10/12	Slight diminution in cellularity of blood islets. Occasional fragmentation of nuclei
	Folic acid†	0.1 mg.											

* No. survived/No. injected. † Injected at same time. ‡ Injected 24 hours before antagonist. § 3 eggs sacrificed for study.
¶ 2 eggs sacrificed for study. ‖ Experiment terminated.

decreased survival time (Series 1). The blood islets from the yolk sacs of such embryos were diminished in both number and size. Frequently the nuclei of the hemopoietic cells in such areas were pyknotic or showed karyolysis and karyorrhexis.

Injection of 0.005 mg. of vitamin B_{12} simultaneously with the inhibitor (Series 2) did not prolong the survival time or modify the histological appearance of the blood islets. As much as 3.75 U.S.P. units (injectable) of purified liver extract (containing the equivalent activity of 2.7 micrograms of vitamin B_{12}) injected 24 hours prior to the administration of the 4-amino-pteroylglutamic acid (Series 3) did not prevent a shortened life span or alteration in the appearance of the yolk sac blood islets. However, when folic acid was given in 12.5 mg. amounts 24 hours prior to the antagonist (Series 4) the blood islets were not decreased in number though their cellularity was somewhat diminished. Pyknosis, karyolysis and karyorrhexis of the nuclei were not present. There was a suggestive increase in survival time.

N^{10}-methyl-pteroic acid in 20 mg. amounts under the conditions of the experiment produced no detectable alteration of the blood islets (Series 5).

Embryonated eggs injected with methyl-4-amino-pteroylglutamic acid in amounts of 0.01 mg. showed a decrease in the number and size of yolk sac blood islets with some fragmentation of the nuclei of the hemopoietic cells (Series 6). These changes were not as marked as those occurring after the use of 4-amino-pteroylglutamic acid. The simultaneous injection of 0.1 mg. of folic acid (Series 7) resulted in less marked cytological changes in the blood islets. There was a slight decrease in the cellularity of the islets and occasional fragmentation of nuclei.

SUMMARY

A new method of study of the effects of folic acid inhibitors is described. Of the 3 antagonists studied, 4-amino-pteroylglutamic acid was the most effective in small doses. There were marked cytological changes in the yolk sac blood islets, characterized by diminution in their size and number with pyknosis, karyolysis and karyorrhexis of many of the remaining nuclei. There was a suggestive shortening of the survival time of the embryos. This effect, as well as that of the

less active methyl-4-amino-pteroylglutamic acid, appeared altered by injections of folic acid but not by liver extract in the doses employed. Vitamin B_{12}, in the amount used, did not alter the apparent effect of 4-amino-pteroylglutamic acid. N^{10}-methyl-pteroic acid in relatively larger doses than the other antagonists caused no detectable changes in the yolk sac blood islets.

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